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[Intervention Review]

Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit

Marija Barbateskovic[1,2], Olav L Schjørring[2,3], Sara Russo Krauss[4], Janus C Jakobsen[2,5,6,7], Christian S Meyhoff[8], Rikke M Dahl[9], Bodil S Rasmussen[2,3], Anders Perner[2,10], Jørn Wetterslev[1,2]

[1]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [2]Centre for Research in Intensive Care, Department 7831, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [3]Department of Anaesthesia and Intensive Care, Aalborg University Hospital, Aalborg, Denmark. [4]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark. [5]Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [6]Department of Cardiology, Holbaek Hospital, Holbaek, Denmark. [7]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [8]Department of Anaesthesia and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark. [9]Department of Anaesthesiology, Herlev Hospital, University of Copenhagen, Herlev, Denmark. [10]Department of Intensive Care, Righospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Contact address: Marija Barbateskovic, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, Copenhagen, DK-2100, Denmark. marija.barbateskovic@ctu.dk.

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ABSTRACT

Background

The mainstay treatment for hypoxaemia is oxygen therapy, which is given to the vast majority of adults admitted to the intensive care unit (ICU). The practice of oxygen administration has been liberal, which may result in hyperoxaemia. Some studies have indicated an association between hyperoxaemia and mortality, whilst other studies have not. The ideal target for supplemental oxygen for adults admitted to the ICU is uncertain. Despite a lack of robust evidence of effectiveness, oxygen administration is widely recommended in international clinical practice guidelines. The potential benefit of supplemental oxygen must be weighed against the potentially harmful effects of hyperoxaemia.

Objectives

To assess the benefits and harms of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU.

Search methods

We identified trials through electronic searches of CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, BIOSIS Previews, CINAHL, and LILACS. We searched for ongoing or unpublished trials in clinical trials registers. We also scanned the reference lists of included studies. We ran the searches in December 2018.

Selection criteria

We included randomized controlled trials (RCTs) that compared higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU. We included trials irrespective of publication type, publication status, and language.

We included trials with a difference between the intervention and control groups of a minimum 1 kPa in partial pressure of arterial oxygen (PaO_2), minimum 10% in fraction of inspired oxygen (FiO_2), or minimum 2% in arterial oxygen saturation of haemoglobin/non-invasive peripheral oxygen saturation (SaO_2/SpO_2).

We excluded trials randomizing participants to hypoxaemia (FiO_2 below 0.21, SaO_2/SpO_2 below 80%, and PaO_2 below 6 kPa) and to hyperbaric oxygen.

Data collection and analysis

Three review authors independently, and in pairs, screened the references retrieved in the literature searches and extracted data. Our primary outcomes were all-cause mortality, the proportion of participants with one or more serious adverse events, and quality of life. None of the trials reported the proportion of participants with one or more serious adverse events according to the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) criteria. Nonetheless, most trials reported several serious adverse events. We therefore included an analysis of the effect of higher versus lower fraction of inspired oxygen, or targets using the highest reported proportion of participants with a serious adverse event in each trial. Our secondary outcomes were lung injury, acute myocardial infarction, stroke, and sepsis.

None of the trials reported on lung injury as a composite outcome, however some trials reported on acute respiratory distress syndrome (ARDS) and pneumonia. We included an analysis of the effect of higher versus lower fraction of inspired oxygen or targets using the highest reported proportion of participants with ARDS or pneumonia in each trial. To assess the risk of systematic errors, we evaluated the risk of bias of the included trials. We used GRADE to assess the overall certainty of the evidence.

Main results

We included 10 RCTs (1458 participants), seven of which reported relevant outcomes for this review (1285 participants). All included trials had an overall high risk of bias, whilst two trials had a low risk of bias for all domains except blinding of participants and personnel.

Meta-analysis indicated harm from higher fraction of inspired oxygen or targets as compared with lower fraction or targets of arterial oxygenation regarding mortality at the time point closest to three months (risk ratio (RR) 1.18, 95% confidence interval (CI) 1.01 to 1.37; I^2 = 0%; 4 trials; 1135 participants; very low-certainty evidence). Meta-analysis indicated harm from higher fraction of inspired oxygen or targets as compared with lower fraction or targets of arterial oxygenation regarding serious adverse events at the time point closest to three months (estimated highest proportion of specific serious adverse events in each trial RR 1.13, 95% CI 1.04 to 1.23; I^2 = 0%; 1234 participants; 6 trials; very low-certainty evidence). These findings should be interpreted with caution given that they are based on very low-certainty evidence.

None of the included trials reported any data on quality of life at any time point.

Meta-analysis indicated no evidence of a difference between higher fraction of inspired oxygen or targets as compared with lower fraction or targets of arterial oxygenation on lung injury at the time point closest to three months (estimated highest reported proportion of lung injury RR 1.03, 95% CI 0.78 to 1.36; I^2 = 0%; 1167 participants; 5 trials; very low-certainty evidence).

None of the included trials reported any data on acute myocardial infarction or stroke, and only one trial reported data on the effects on sepsis.

Authors' conclusions

We are very uncertain about the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU on all-cause mortality, serious adverse events, and lung injuries at the time point closest to three months due to very low-certainty evidence. Our results indicate that oxygen supplementation with higher versus lower fractions or oxygenation targets may increase mortality. None of the trials reported the proportion of participants with one or more serious adverse events according to the ICH-GCP criteria, however we found that the trials reported an increase in the number of serious adverse events with higher fractions or oxygenation targets. The effects on quality of life, acute myocardial infarction, stroke, and sepsis are unknown due to insufficient data.

PLAIN LANGUAGE SUMMARY

Supplemental oxygen for adults admitted to the intensive care unit

Review question

We set out to assess whether more supplemental oxygen is better than less supplemental oxygen for adults admitted to the intensive care unit (ICU).

Background

Adults admitted to the ICU are critically ill and are at high risk of dying. Oxygen supplementation, or therapy, is given to most adults admitted to ICU, and many are mechanically ventilated. Severe illness can result in a lack of oxygen in the blood, known as hypoxaemia, which puts patients at risk of low tissue levels of oxygen (hypoxia) and organ failure. The use of sedatives and strong pain relief medications can also depress breathing and therefore oxygen levels.

The practice of supplemental oxygen administration has been liberal, possibly resulting in too much oxygen, known as hyperoxia. Despite a lack of robust evidence of effectiveness, supplemental oxygen administration has been widely recommended in international clinical practice guidelines. However, a new guideline recommends against high oxygen levels as some, but not all, clinical studies have indicated a link between hyperoxaemia and an increased risk of dying. The potential benefit of supplemental oxygen must be weighed against the potentially harmful effects of hyperoxaemia.

Study characteristics

We identified 10 randomized controlled trials (studies where participants are randomly allocated to either an experimental or a control group) involving 1458 participants up to December 2018. Seven of the trials (1285 participants) provided findings on the number of deaths, serious adverse events, and lung injuries in the three months following oxygen therapy in the ICU. Lung injury was measured according to participants developing acute respiratory distress syndrome or pneumonia. Five trials included adults admitted to an ICU caring for patients with a range of serious health conditions and one to a surgical ICU. Two trials involved adults with traumatic brain injury; one trial adults after cardiac arrest and resuscitation; and one trial adults with stroke. All participants in six trials received invasive mechanical ventilation directly through a tube into the main airway. In one trial some of the participants were on mechanical ventilation, whilst others received non-invasive oxygen administration. Three trials involved adults receiving non-invasive oxygen. All trials compared more with less oxygen, however using very different levels of oxygen supplementation. Oxygen therapy was given for timeframes ranging from one hour to the length of hospital admission.

Key results

We are uncertain about the effects of higher levels of oxygen as our findings are based on very low-certainty evidence. We found no evidence for a beneficial effect of higher compared with lower supplemental oxygen levels for adults admitted to ICU. Higher levels of oxygen may have increased the risk of death (4 trials; 1135 participants) and serious adverse events (6 trials; 1234 participants). There was no evidence of a difference in lung injuries with the use of higher supplemental oxygen compared with lower supplemental oxygen, but the evidence is very uncertain (5 trials; 1167 participants). None of the included trials reported on quality of life at any time point, acute myocardial infarction, and stroke. Only one trial reported on sepsis.

Certainty of the evidence

The numbers of participants enrolled in the trials were too small to permit a definitive judgement about the review findings. The trials varied in the types of illness of the participants, their associated clinical care, disease severity, the targets for how much oxygen was given, and for how long. Two of the trials had a low risk of bias other than for lack of blinding of participants and personnel. Overall all included trials had a high risk of bias.

Summary of findings for the main comparison. Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU

Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU

Patient or population: adults admitted to the ICU
Setting: trials were conducted in ICU departments in Europe (n = 5); Iran (n = 2); New Zealand (n = 1); Australia, New Zealand, France (n = 1); and Japan (n = 1)
Intervention: higher fraction of inspired oxygen or targets of arterial oxygenation
Comparison: lower fraction of inspired oxygen or targets of arterial oxygenation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower FiO_2 or targets of arterial oxygenation	Risk with higher FiO_2 or targets of arterial oxygenation				
All-cause mortality follow-up: range 1 month to 3 months	Study population		RR 1.18 (1.01 to 1.37)	1135 (4 RCTs)	⊕⊖⊖⊖ Very low[1]	-
	331 per 1000	391 per 1000 (334 to 453)				
Proportion of participants with 1 or more serious adverse events according to International Conference on Harmonisation Good Clinical Practice (ICH-GCP) follow-up: range 3 to 90 days	Study population		RR 1.13 (1.04 to 1.23)	1234 (6 RCTs)	⊕⊖⊖⊖ Very low[2]	Reported results are derived by taking the highest proportion reported in each trial which addresses the lowest possible proportion of participants with 1 or more serious adverse events. The following outcomes and numbers of trials and participants have been included: mortality: 3 trials, 701 participants; pneumonia: 1 trial, 65 participants; proportion of participants with 1 or more serious adverse events: 1 trial, 434 participants; mechanical ventilation (reported as a poor outcome): 1 trial, 34 participants. Meta-analysis from the analysis cumulating all reported serious adverse events which ad-
	430 per 1000	486 per 1000 (447 to 529)				

						dress the highest possible reported proportion of participants with 1 or more serious adverse events showed RR 1.08, 95% CI 0.99 to 1.18.
Quality of life (any valid scale such as the 36-item Short Form Health Survey (SF-36))	Study population -	-	Not estimable	(0 studies)	-	No studies reported this outcome.
Lung injury diagnosed after randomization (composite outcome) follow-up: range 4 to 23 days	Study population 128 per 1000	132 per 1000 (100 to 174)	RR 1.03 (0.78 to 1.36)	1167 (5 RCTs)	⊕⊖⊖⊖ Very low[3]	Reported results are derived by taking the highest proportion reported in each trial which addresses the lowest possible proportion of participants with 1 or more lung injuries. The following outcomes and numbers of trials and participants have been included: ARDS: 2 trials, 223 participants; pneumonia: 3 trials, 944 participants. Meta-analysis from the analysis cumulating all reported lung injuries which address the highest possible reported proportion of participants with 1 or more lung injuries showed RR 0.99, 95% CI 0.75 to 1.30.
Acute myocardial infarction diagnosed after randomization	Study population -	-	Not estimable	(0 studies)	-	No studies reported this outcome.
Stroke diagnosed after randomization	Study population -	-	Not estimable	(0 studies)	-	No studies reported this outcome.
Severe sepsis diagnosed after randomization follow-up: 3 days	Study population 50 per 1000	94 per 1000 (46 to 189)	RR 1.87 (0.93 to 3.87)	445 (1 study)	⊕⊖⊖⊖ Very low[4]	Meta-analysis was not conducted, as only 1 trial reported on sepsis.

*__The risk in the intervention (higher) group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). __The risk in the control (lower) group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ARDS: acute respiratory distress syndrome; **CI:** confidence interval; **FiO_2:** fraction of inspired oxygen; **ICU:** intensive care unit; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[1]Downgraded three levels: one level because of risk of bias, as only one trial was overall low risk of bias except for blinding of participants and personnel (performance bias); one level because of differences in inspiratory oxygen fraction and target of arterial oxygenation in the experimental and control groups between trials; and one level because the optimal information size (OIS) was not reached. Required information size (RIS) is 2623 participants. RIS = OIS when $I^2 = 0$ and alpha is adjusted for multiple outcomes.
[2]Downgraded three levels: one level because of risk of bias, as only one trial was overall low risk of bias except for blinding of participants and personnel (performance bias); one level because of differences in inspiratory oxygen fraction and target of arterial oxygenation in the experimental and control groups between trials; and one level because the optimal information size (OIS) was not reached. Required information size (RIS) is 1577 participants. RIS = OIS when $I^2 = 0$ and alpha is adjusted for multiple outcomes.
[3]Downgraded three levels: one level because of risk of bias, as only one trial was overall low risk of bias except for blinding of participants and personnel (performance bias); one level because of differences in inspiratory oxygen fraction and target of arterial oxygenation in the experimental and control groups between trials; and one level because the optimal information size (OIS) was not reached. Required information size (RIS) is 7656 participants. RIS = OIS when $I^2 = 0$ and alpha is adjusted for multiple outcomes.
[4]Downgraded three levels: one level because of risk of bias; one level because we cannot reject inconsistency due to the inclusion of only one trial; and one level because the optimal information size was not reached.

BACKGROUND

Description of the condition

Hypoxaemia refers to lack of oxygen in the blood and is usually defined in terms of partial pressure of arterial oxygen (PaO_2) or arterial oxygen saturation of haemoglobin (SaO_2) (O'Driscoll 2017). Additionally, the non-invasive peripheral oxygen saturation (SpO_2) measured by pulse oximetry is routinely used. Hypoxaemia refers directly to the levels of oxygen in the blood, whilst the term hypoxia is defined as the lack of oxygen at a cellular level, for example tissues, organs, alveoli, or the body as a whole (O'Driscoll 2017).

In healthy individuals, the normal range for PaO_2 at sea level is 80 mmHg to 100 mmHg (Kratz 2004), with a general decrease with age (Crapo 1999). There is no clear definition of hypoxaemia; the most widely used definitions are a PaO_2 below 60 mmHg or a SaO_2 below 90% (O'Driscoll 2017). However, oxygenation targets below the normal range, and even defined as hypoxaemic, are recommended in adults who are mechanically ventilated with acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU) targeting PaO_2 of 55 mmHg to 80 mmHg or SpO_2 of 88% to 95% (ARDS Network 2000; Brower 2004).

In adults admitted to the ICU, hypoxaemia is a common clinical manifestation of inadequate gas exchange in the lungs (Petersson 2014). The condition can arise primarily from four different mechanisms: hypoventilation, ventilation or perfusion (V/Q) mismatch, intrapulmonary right-to-left blood shunting, or diffusion impairment, or a combination of these (Petersson 2014; Roussos 2003). Hypoventilation in the ICU is typically caused by an acute depression of the central nervous system, either through administration of sedative or analgesic agents, or due to critical illness with indirect (e.g. circulatory, hypoxic, or hypercapnic failure) or direct (e.g. traumatic brain injury, intracranial haemorrhage, or meningoencephalitis) cerebral affection. Hypoxaemia due to hypoventilation is always accompanied by hypercapnia since hypoventilation affects the alveolar clearance of carbon dioxide to a larger degree than the alveolar oxygenation, and hypoventilation does not affect the alveolar-arterial gradient (Petersson 2014; Roussos 2003). V/Q mismatch with a low V/Q ratio evolves when ventilation in certain lung regions is disproportionally decreased as compared to perfusion. This is seen in various conditions (Petersson 2014), including pneumonia, ARDS, pulmonary oedema, and chronic obstructive pulmonary disease (COPD) (Kent 2011). The impact of a low V/Q ratio is partially compensated by physiological hypoxic pulmonary vasoconstriction in the affected segments of the lung (Rodríguez-Roisin 2005). V/Q mismatch with a high V/Q ratio evolves when perfusion in certain lung regions is disproportionally decreased as compared to ventilation, as is classically seen in pulmonary embolism (Petersson 2014), but is also prevalent in COPD, Wagner 1977, and ARDS (Donahoe 2011). Intrapulmonary shunting is the consequence of complete V/Q mismatch with abolished ventilation which allows the passing of blood through sections of the pulmonary vascular bed without being oxygenated. This is seen in all types of pulmonary atelectasis (including absorption atelectasis) and is especially prevalent in ARDS and pneumonia (Petersson 2014). V/Q mismatch and intrapulmonary shunting are the most common causes of hypoxaemia in the ICU (Petersson 2014). Diffusion impairment occurs when the diffusion pathway for oxygen from the alveolar space to the pulmonary capillaries is pathologically increased, either acutely as seen in pneumonia, pulmonary oedema, or ARDS, or chronically as seen in the large group of interstitial lung diseases (Petersson 2014).

Description of the intervention

Administration of supplemental oxygen, defined as the fraction of inspired oxygen (FiO_2) above 0.21, is a frequent intervention in adults admitted to the ICU. Oxygen is often administered during acute conditions in the pre-hospital setting and during hospital admission. Adults admitted to the ICU often receive mechanical ventilation, and oxygen support to correct or prevent hypoxaemia. Treatment is usually a combination of ventilatory and non-ventilatory strategies (Esan 2010; Raoof 2010), where the aim is to reduce morbidity and mortality associated with hypoxaemia by restoring arterial oxygenation to normal values. Due to the administration of oxygen, adults often achieve supranormal levels of PaO_2 (de Graaff 2011; de Jonge 2008; Eastwood 2012; Itagaki 2015; Kraft 2018; Suzuki 2013; Zhang 2016).

Oxygen strategies used to treat hypoxaemia in adults admitted to the ICU are associated with harm in some studies, possibly because adults who receive oxygen in the ICU are the most ill, but it may also be that 'too much' oxygen is as harmful as 'too little' (Kallet 2013). The harms associated with lung injury caused by mechanical ventilation as well as by oxygen toxicity following high FiO_2 may exceed the benefit of normalizing oxygenation (PaO_2 and SaO_2).

How the intervention might work

The purpose of oxygen therapy is to increase oxygen delivery to tissues. Tissue hypoxia can cause cell death, but the precise level at which this occurs has not been determined, and the level may differ between tissues, organs, and individuals (O'Driscoll 2017).

Supplemental oxygen therapy has several potential advantages including maintenance of delivery of oxygen to tissues and prevention of organ dysfunction followed by anoxic injury (Budinger 2013). Several additional beneficial effects of supplemental oxygen have been proposed and include: induction of antioxidant enzymes, anti-inflammatory proteins, anti-inflammatory cytokines and certain growth factors; reduced postoperative infections, neutrophil activation, and markers of cerebral tissue breakdown; anti-apoptotic effects in brain and myocardium; normalization of cerebral extracellular homeostasis; and stabilization of the blood-brain barrier (Tan 2014).

High inspiratory oxygen concentrations have been associated with adverse outcomes in emergency medical conditions in patients with exacerbation of COPD (Austin 2010); after resuscitation after cardiac arrest (Kilgannon 2010); in patients with myocardial infarction (Cabello 2016); and in patients with traumatic brain injury (Brenner 2012). Additionally, treating perioperative adults with high FiO_2 may be associated with increased mortality without reducing surgical site infections in surgical adults (Wetterslev 2015). These adverse outcomes may be caused by postoperative pulmonary complications due to atelectasis formation, Benoit 2002; Rothen 1995a; Rothen 1995b, or pulmonary formation of reactive oxygen species (Chow 2003; Helmerhorst 2015; Kallet 2013). However, they may also be related to decreased local blood flow on normal and non-diseased vasculature induced by hyperoxaemic vasoconstriction (Sjöberg 2013), which has been

described in the vascular system, for example in the heart and brain (Kenmure 1971; Watson 2000).

Knowledge about cell biology also suggests that oxygen might have harmful effects. Prolonged exposure to hyperoxia causes lung injury, which is thought to be caused by the production and accumulation of reactive oxygen species that overwhelm natural antioxidant defences and destroy cellular structures (Kallet 2013). Exposure to hyperoxia is associated with a boost in the production of reactive oxygen species, which eventually may overwhelm the cell repair processes, thereby causing cell injury (Crapo 1986). It has been proposed that reactive oxygen species may trigger apoptosis within pulmonary cells leading to necrosis, thereby causing an inflammation which damages lung tissue further (Zaher 2007).

Mechanical ventilation may in itself also be associated with complications including increased risk of pneumonia, impaired cardiac performance, and neuromuscular problems relating to sedation and muscle relaxants (Whitehead 2002). Also, applying pressure to the lungs can cause damage, which is known as ventilator-induced lung injury. Ventilator-associated lung injury has been shown to be augmented by hyperoxia in animal studies (Bailey 2003; Helmerhorst 2017b; Sinclair 2004).

Why it is important to do this review

The mainstay treatment for hypoxaemia is supplemental oxygen therapy, which is given to the vast majority of adults admitted to the ICU. It is estimated that 2 to 3 million adults yearly require mechanical ventilation in the ICU in high-income countries (Adhikari 2010), and is associated with morbidity, Kahn 2010, and mortality (Metnitz 2009; Wunsch 2010).

The current practice of oxygen administration has usually been more liberal and may result in hyperoxaemia or high partial tension of oxygen in the lungs (de Graaff 2011; de Jonge 2008; Itagaki 2015; Kraft 2018; Panwar 2013; Rachmale 2012; Suzuki 2013; Zhang 2016). Some studies have indicated an association between hyperoxaemia and mortality (Dahl 2015; Helmerhorst 2017a; Kilgannon 2010; Meyhoff 2012; Zhang 2016), whilst other studies have not (Bellomo 2011; Eastwood 2012; Kraft 2018; Raj 2013; Young 2012). Two meta-analyses of observational data found an association between hyperoxaemia and mortality after cardiac arrest, stroke, and traumatic brain injury (Damiani 2014), and overall across critically ill adults (Helmerhorst 2015). Permissive hypoxaemia has been studied by Gilbert-Kawai and colleagues (Gilbert-Kawai 2014), who compared permissive hypoxaemia to normoxaemia in critically ill adults in a systematic review but found no relevant randomized controlled trials (RCTs).

Although the possible adverse effects of hyperoxaemia are known, prevention of hypoxia through hyperoxaemia seems to be prioritized (Pannu 2016). The ideal target oxygenation for adults admitted to the ICU is uncertain due to limited evidence from RCTs. Despite a lack of robust evidence of effectiveness, oxygen administration is widely recommended in international clinical practice guidelines (AARC 2002; ARC 2014; Dellinger 2013; O'Driscoll 2017). However, it appears that a change towards a more restrictive approach is under way (Chu 2018; Siemieniuk 2018). Panwar and colleagues, Panwar 2015, and Girardis and colleagues, Girardis 2016, published data on RCTs comparing higher with lower oxygenation targets in adults admitted to the ICU, and Asfar and colleagues, Asfar 2017, published data on an RCT comparing high FiO_2 with lower oxygenation targets throughout the first 24 hours of ICU admission in adults with septic shock. Additional RCTs comparing high versus low targeted oxygen therapy in the critically ill are ongoing and may soon be published (NCT02321072; NCT03174002).

Oxygen is a common intervention in adults admitted to ICU and might have beneficial effects as well as harmful effects (Hafner 2015). The potential benefit of supplemental oxygen must be weighed against the potentially harmful effects of hyperoxaemia (Jakobsen 2013).

OBJECTIVES

To assess the benefits and harms of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation in adults in intensive care units.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs, irrespective of publication status, reported outcomes, publication date, and language.

We included unpublished trials only if methodological descriptions and trial data were provided by direct contact with trial authors or in written form.

We excluded randomized cross-over trials and quasi-randomized trials.

Types of participants

We included any adult aged 18 years or older admitted to the ICU. We only included participants if they were admitted to the ICU when randomization was allocated.

Types of interventions

We included trials having a clear differentiation of participants randomized to either a high-target (liberal) or a low-target (conservative) oxygenation strategy. Both mechanically ventilated and non-mechanically ventilated adults were eligible for inclusion. In order to include all relevant trials, we did not use predefined arbitrary thresholds of oxygenation for the two groups.

Intervention group: adults receiving a high-target (liberal) oxygenation strategy administered by any device, the aim of which was exposure to hyperoxia in the lungs, either by high FiO_2 or high-target PaO_2 or SaO_2/SpO_2.

Control group: adults receiving a low-target (conservative) oxygenation strategy administered by any device, the aim of which was to minimize exposure to hyperoxia in the lungs and reduce exposure to high FiO_2 or high-target PaO_2 or SaO_2/SpO_2.

Eligible trials were required to have a difference between the intervention and control groups of minimum 1 kPa in PaO_2, minimum 10% in FiO_2, or minimum 2% in SaO_2/SpO_2, either as aimed or achieved saturation or target. We only required one of these separation criteria to be fulfilled (PaO_2, SaO_2 or FiO_2), either aimed or achieved, for the trial to be eligible for inclusion.

We excluded trials/groups randomized to hypoxaemia (FiO_2 below 0.21, SaO_2/SpO_2 below 80%, and PaO_2 below 6 kPa). We furthermore excluded interventions with hyperbaric oxygen.

Types of outcome measures

Primary outcomes

1. All-cause mortality at the time point closest to three months.
2. Proportion of participants with one or more serious adverse events, defined as a dichotomous outcome according to participants having at least one serious adverse event or none at time point closest to three months. We defined a serious adverse event as any untoward medical occurrence that: resulted in death; was life-threatening; required hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability; or jeopardized the participant (ICH-GCP 1997). We performed two analyses on the proportion of participants with one or more serious adverse events according to the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) (ICH-GCP 1997). We considered all other adverse events as non-serious.
3. Quality of life (any valid scale such as the 36-item Short Form Health Survey (SF-36)) at the time point closest to three months.

Secondary outcomes

1. Lung injury diagnosed after randomization (composite outcome) at the time point closest to three months. This composite outcome was defined as either: ARDS (defined by the onset of a known clinical insult within one week or acute worsening of respiratory symptoms; chest imaging; origin of oedema; and oxygenation may be mild, moderate, or severe (ARDS Definition Task Force 2012), or as defined by trialists); pulmonary fibrosis (defined as evolved from any cause or as defined by trialists); or pneumonia (defined as pneumonia occurring 48 hours or more after admission in non-intubated participants or pneumonia arising more than 48 to 72 hours after endotracheal intubation (ATS 2005), or as defined by trialists). As a secondary analysis, we analysed each component of the composite outcome separately. We performed two analyses on the proportion of participants with one or more lung injury.
2. Acute myocardial infarction diagnosed after randomization at the time point closest to three months (defined as the demonstration of myocardial cell death due to significant and sustained ischaemia (Thygesen 2012), or as defined by trialists).
3. Stroke diagnosed after randomization at the time point closest to three months (defined as central nervous system infarction, ischaemic stroke, silent central nervous system infarction, intracerebral haemorrhage, stroke caused by intracerebral haemorrhage, silent cerebral haemorrhage, subarachnoid haemorrhage, stroke caused by subarachnoid haemorrhage, stroke caused by cerebral venous thrombosis, and stroke not otherwise specified (Sacco 2013), or as defined by trialists).
4. Severe sepsis diagnosed after randomization at the time point closest to three months (defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (Dellinger 2013), or as defined by trialists).

Search methods for identification of studies

Electronic searches

We identified eligible RCTs through literature searching with systematic and sensitive search strategies specifically designed to identify relevant RCTs without restrictions to language, publication year, and journal.

We searched the following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 12, 2018) (Appendix 1);
2. MEDLINE (Ovid, 1946 to 20 December 2018) (Appendix 2);
3. Embase (Ovid, 1974 to 20 December 2018) (Appendix 3);
4. Science Citation Index (Web of Science, 1900 to 20 December 2018) (Appendix 4);
5. BIOSIS Previews (Web of Science, 1969 to 20 December 2018) (Appendix 5);
6. Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO, 1981 to 20 December 2018) (Appendix 6);
7. Latin American and Caribbean Health Science Information database (LILACS) (1982 to 20 December 2018) (Appendix 7).

Searching other resources

We manually screened the reference lists of included trial reports, reviews, relevant papers, randomized and non-randomized trials, and editorials for potentially relevant trials.

Furthermore, we searched for ongoing and unpublished trials using the following trial registers:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) (searched 21 December 2018);
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) (searched 21 December 2018);
3. EU Clinical Trials Register (www.clinicaltrialsregister.eu/) (searched 21 December 2018);
4. Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au/) (searched 21 December 2018).

Data collection and analysis

We used the following methods for data collection and data analyses.

Selection of studies

Three review authors (MB, OLS or SRK), independently and in pairs, screened each title and abstract of all reports identified by the searches. We obtained the full texts of those reports deemed potentially relevant and assessed these for inclusion in the review. Any disagreements were resolved by consensus or by consulting another review author (JW) when necessary.

Data extraction and management

Three review authors (MB, OLS or SRK), independently and in pairs, extracted predefined data of the included trials using a data collection form that was specifically designed and piloted by the review team (Appendix 8). We collected the following data:

1. trial: country, duration of the trial, date of publication, and type of trial;
2. participants: numbers randomized, numbers analysed, numbers lost to follow-up or withdrawn, type of population, mean or median age, sex, inclusion criteria, and exclusion criteria;
3. interventions: intervention, comparator, and concomitant interventions;
4. outcomes: predefined primary and secondary outcomes.

Any disagreements concerning the extracted data were resolved by discussion or by consulting a third review author (JW) when necessary. Where required, we contacted corresponding authors to clarify issues relating to data reporting or if further study details were needed.

Assessment of risk of bias in included studies

At least two review authors (MB, OLS or SRK) independently assessed the methodological quality of each included trial, as defined by the design of the trial and reporting. Any disagreements were resolved by discussion. We assessed the risk of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), employing the criteria described in Appendix 9.

We assessed the following risk of bias domains for all included trials: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other potential sources of bias, and overall risk of bias. In addition, we assessed the domains blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting for each outcome, which permitted an assessment of the risk of bias for each result. Based on this assessment, we defined the included trials and each outcome result as low risk of bias if all bias domains were judged as at low risk of bias.

We provided a summary assessment of the risk of bias across trials and for each important outcome (across domains) by preparing a 'Summary of findings' table, 'Risk of bias' graph, and a 'Risk of bias' summary figure (Higgins 2011a).

Measures of treatment effect

We calculated the risk ratio (RR) with 95% confidence interval (CI) and Trial Sequential Analysis (TSA) CI, adjusted for multiple outcomes, sparse data, and repetitive testing for dichotomous outcomes. For continuous outcomes, we planned to include both end scores and change scores in the analyses; we would use end scores if both were reported. We planned to calculate the mean difference (MD) and standardized mean difference (SMD) with 95% CIs and TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing for continuous outcomes.

Unit of analysis issues

Had we found a multi-arm trial that compared, for example, three different oxygenation targets, we would have combined the two experimental intervention groups of the study (if they each fulfilled the minimum difference compared with the control group of 1 kPa in PaO_2, 10% in FiO_2, and 2% in SaO_2/SpO_2) into a single group and compared these to the control group. If only one of the experimental groups fulfilled the minimum difference to the control, we would have compared this group to the control group.

For multi-arm trials that compare, for example, three different oxygenation targets, where the control group is the middle group, and the minimum difference in oxygenation target was fulfilled, we planned to compare the higher oxygenation group to the control group, as the lower group would be excluded due to being randomized to an extreme permissive hypoxaemia.

For cluster-randomized trials, we planned to define the ICU as the unit of allocation, and we would use the generic inverse-variance method in Review Manager 5 to calculate effect estimates for these trials (Review Manager 2014).

Dealing with missing data

We contacted trial investigators of the original reports for important missing data.

We did not impute missing data for any outcomes in the primary analysis, and we did not use intention-to-treat data if the original report did not contain such data.

If trial reports did not report standard deviations (SD), we would calculate the SDs using data from the trial report if possible.

We used imputed data in the sensitivity analysis for dichotomous and continuous outcomes (see Sensitivity analysis).

Assessment of heterogeneity

We assessed signs of heterogeneity by visual inspection of the forest plots.

We assessed the presence of statistical heterogeneity using the Chi^2 test with significance set at $P < 0.10$, and by measuring the quantities of heterogeneity using the I^2 statistic (Higgins 2003). Overall, we considered an I^2 statistic of 0% to 40% as not important, 30% to 60% as moderate, 50% to 90% as substantial, and 75% to 100% as considerable heterogeneity (Higgins 2011a). High statistical heterogeneity is generally more prevalent when meta-analysing continuous outcomes (Alba 2016). Because we anticipated large clinical heterogeneity as well as statistical heterogeneity, we generally preferred to use a random-effects model. However, if one or two trials dominate the acquired evidence (e.g. with more than 80% of the randomized participants) (Higgins 2002; MAGIC 2002; Woods 2002), the random-effects model may grossly overestimate the intervention effect; in such a situation, we would primarily report the results from a fixed-effect model. Hence, we primarily reported the result from the model with the most conservative point estimate of the two (Jakobsen 2014a), being the estimate closest to zero effect. If the two estimates were approximately equal, we used the estimate with the widest CI.

We explored potential clinical heterogeneity by conducting the prespecified subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We planned to visually assess funnel plots for signs of asymmetry if an analysis included 10 or more trials (Higgins 2011a; Jakobsen 2014a).

We planned to test asymmetry within dichotomous outcomes using the Harbord test (Harbord 2006), and for continuous outcomes using the asymmetry test (Egger 1997). We would also use adjusted rank correlation (Begg 1994).

Data synthesis

Meta-analysis

We undertook the systematic review according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* and the eight-step assessment suggested by Jakobsen and colleagues (Higgins 2011a; Jakobsen 2014a), including TSA and calculation of Bayes factors. We performed meta-analysis of outcomes with comparable effect measures where more than one trial was included. If clinical and statistical heterogeneity were large or unexpected, we planned to reconsider performing meta-analysis. We used the statistical software Review Manager 5 provided by Cochrane and the TSA software version 0.9 CTU to meta-analyse data (Review Manager 2014; TSA 2011).

Assessment of significance

We assessed our intervention effects with both random-effects model meta-analyses, Deeks 2010; DerSimonian 1986; Mantel 1959, and fixed-effect model meta-analyses, DeMets 1987; Mantel 1959, and reported the most conservative estimate, being the point estimate closest to no effect or the estimate with the widest CI.

We used three co-primary outcomes and therefore considered $P \leq 0.025$ as statistically significant analysing the primary outcomes (Jakobsen 2014a; Jakobsen 2016). We used four co-secondary outcomes and therefore considered $P \leq 0.02$ as statistically significant analysing the secondary outcomes (Jakobsen 2014a). We used the eight-step procedure to assess if the thresholds for significance were crossed (Jakobsen 2014a).

Trial Sequential Analysis (TSA)

The chance of type I error (a false-positive finding) is increased when multiple testing is done (e.g. when analysing multiple primary and secondary outcomes or repeated testing of the data). In small studies, notably for binary outcomes, type I error is likely because the effect estimates tend to be more unstable (Mascha 2015). In meta-analyses the chance of finding a type I error is increased when they are updated over time when new trials are added (Mascha 2015). Cochrane recommends updating systematic reviews when, for example, new trials are available that will or might change the findings or credibility of the review, making it highly important to adjust for the multiplicity issue.

Current practice often uses a 0.05 significance criterion each time meta-analyses are updated, thus increasing the overall chance of a type I error (Mascha 2015). In addition, type II error (the probability of missing true findings) is a problem in many meta-analyses due to sparse data. Statistically significant meta-analyses with few participants have low reliability, and the interventional effect is often overrated (Turner 2013). In a random sample of 50 meta-analyses of anaesthesiology interventions with dichotomous outcome variables, Imberger and colleagues found 88% of the meta-analyses to be underpowered, meaning that although significant at $P < 0.05$, the meta-analyses should have included more participants (Imberger 2015). Furthermore, only 32% of the meta-analyses preserved the risk of type I error at 5% or less when powered for detecting a relative risk of 20% between groups (Imberger 2015).

Consequently, cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (Brok 2008; Brok 2009; Higgins 2011b; Imberger 2015; Mascha 2015; Pogue 1997; Terkawi 2016; Thorlund 2009; Wetterslev 2008), and TSA, Imberger 2016; TSA 2011, can be applied to assess this risk (Gluud 2011). The required information size and the required number of trials (i.e. the number of participants and trials needed in a meta-analysis to detect or reject an a priori prespecified realistic intervention effect) can be calculated to minimize random errors (Kulinskaya 2014; Wetterslev 2009). The required information size takes into account the event proportion in the control group, the assumption of a plausible relative risk reduction (RRR), and the heterogeneity variance of the meta-analysis (Turner 2013; Wetterslev 2009). Trial Sequential Analysis enables testing for significance to be conducted each time a new trial is included in the meta-analysis. On the basis of the required information size and the required number of trials, trial sequential monitoring boundaries can be constructed. This enables determination of the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size (Imberger 2015; Mascha 2015; Terkawi 2016; Wetterslev 2008).

Firm evidence for benefit or harms may be established if the trial sequential monitoring boundary is crossed before reaching the required information size, in which case further trials may turn out to be superfluous. In contrast, if the boundary is not surpassed, the determination can be made that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. TSA can also assess firm evidence for lack of the postulated intervention effect, which occurs when the cumulative Z-score crosses the trial sequential monitoring boundaries for futility.

We used relatively conservative estimations of the anticipated intervention effect estimates in order to reduce the risk of random error (Jakobsen 2014a). Large anticipated intervention effects lead to small required information sizes, and the thresholds for significance will be less strict after the information size has been reached (Jakobsen 2014a).

We analysed all primary and secondary outcomes with TSA. We estimated the diversity (meta-analytic heterogeneity-adjustment factor) and calculated the required information size (Wetterslev 2009), based on the proportion of participants with an outcome in the control group. In addition, we used a family-wise error rate (FWER) of 5% (Jakobsen 2014a), leading to a statistical significance level of 2.5% for each of the co-primary outcomes, a beta of 10%, and a diversity (D^2), Wetterslev 2009, suggested by the trials in the meta-analysis (Jakobsen 2014a). We have presented TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing (Gluud 2011). As a sensitivity analysis, we used a diversity of 20% if the actual measured heterogeneity was zero because in this case heterogeneity will most likely increase when further trials are added until the required information size is reached. As anticipated intervention effects for the primary and secondary outcomes in the TSA, we used realistic a priori RRR of 20% or a 20% relative risk increase (RRI). Furthermore, we used an RRR or an RRI based on the confidence limit closest to null effect in the 95% CI in the traditional meta-analysis.

Bayes factor

A low P value indicates that an observed result is unlikely given the null hypothesis is true (Jakobsen 2014b). In meta-analyses, a low P value can be misleading if there is also a low probability that data are compatible with an anticipated intervention effect (e.g. RRR or RRI of 20%). Bayes factor may be used to consider whether the probability that the actual measured difference in the effect of the compared interventions results from an a priori anticipated 'true' difference (Jakobsen 2014a). We calculated Bayes factors for the co-primary outcomes, which is the ratio between the probability of the meta-analysis result given the null hypothesis (H_0) is true divided by the probability of the meta-analysis result given the alternative hypothesis (H_A) is true using a Bayes factor calculator (Bayes factor calculator 2014). A high Bayes factor indicates that the meta-analysis result is produced by an intervention effect that is lower than the anticipated intervention effect, and thus the meta-analysis result should be interpreted with caution. A low Bayes factor together with a low P value corresponds to a high probability of an intervention effect similar to or greater than the anticipated intervention effect used in the calculation of the required information size. A Bayes factor less than 0.1 (a tenfold higher likelihood of compatibility with the alternative hypothesis than with the null hypothesis) has been suggested as the threshold for significance (Jakobsen 2014b).

Subgroup analysis and investigation of heterogeneity

We meta-analysed all included trials regardless of oxygenation strategy (PaO_2, SaO_2, SpO_2, FiO_2). We believed a meta-analysis of the specified strategies was feasible, as the amount of oxygen absorbed overlaps to a great extent. Whether FiO_2 is raised, or the aim is a higher target PaO_2, the result is that more oxygen is delivered, and the PaO_2 will be elevated in both strategies. However, we recognize that, especially in adults with ARDS, there are individuals where it would be extremely difficult to reach a predefined target of PaO_2 by either strategy, but both strategies would certainly expose the lungs to high oxygen levels, whilst other individuals may subsequently develop different PaO_2 levels with the two strategies.

We sought to determine if the efficacy and safety of the treatment options were influenced by types of ICU populations and type of oxygen administration.

We performed the following subgroup analyses.

1. According to different types of oxygen interventions:
   a. oxygen level defined by FiO_2 (as defined and set by trialists);
   b. oxygenation target measured using PaO_2 (as defined by trialists);
   c. oxygenation target measured using SaO_2 or SpO_2 (as defined by trialists);
   d. oxygenation target measured using either PaO_2 or SaO_2 or SpO_2 (as defined by trialists).
2. According to FiO_2 or oxygenation/target in the higher-oxygen-administration group:
   a. low targets defined as FiO_2 of 0.5 or lower or PaO_2 of 10 kPa or lower or SaO_2/SpO_2 of 95% or lower;
   b. high targets defined as FiO_2 above 0.5 or PaO_2 above 10 kPa or SaO_2/SpO_2 above 95%.
3. According to FiO_2 or oxygenation/target in the lower-oxygen-administration group:
   a. low targets defined as FiO_2 between or at 0.21 to 0.30 or PaO_2 between or at 6 kPa to 8 kPa or SaO_2/SpO_2 between or at 85% to 90%;
   b. high targets defined as FiO_2 above 0.30 to 0.40 or PaO_2 above 8 kPa to 10 kPa or SaO_2/SpO_2 above 90%.
4. According to ICU population:
   a. medical;
   b. surgical;
   c. mixed;
   d. adults with any respiratory failure;
   e. adults with any cerebral disease;
   f. adults with any heart disease;
   g. adults with any trauma;
   h. adults with COPD.
5. According to oxygen delivery system:
   a. invasive mechanical ventilation with endotracheal tube;
   b. any non-invasive oxygen administration.

Sensitivity analysis

To assess the potential impact of bias, we planned to conduct a sensitivity analysis for each outcome excluding trials with overall 'high risk of bias'.

To assess the potential impact of the missing data for dichotomous outcomes, we performed the two following analyses:

1. 'best-worst-case' scenario: we assumed that all participants lost to follow-up in the experimental group survived, had no serious adverse event, and had no morbidity; and all participants with missing outcomes in the control group did not survive, had a serious adverse event, and had morbidity;
2. 'worst-best-case' scenario: we assumed that all participants lost to follow-up in the experimental group did not survive, had a serious adverse event, and had morbidity; and all participants with missing outcomes in the control group did survive, had no serious adverse event, and had no morbidity.

Results from both scenarios are presented in the review.

To assess the potential impact of the missing data for continuous outcomes, we planned to perform the two following analyses:

1. 'best-worst-case' scenario: we assumed that all participants lost to follow-up in the experimental group had mean (from participants with follow-up) + 2 × SD, and all participants with missing outcomes in the control group had mean (from participants with follow-up) − 2 × SD;
2. 'worst-best-case' scenario: we assumed that all participants lost to follow-up in the experimental group had mean (from participants with follow-up) − 2 × SD, and all participants

with missing outcomes in the control group had mean (from participants with follow-up) + 2 × SD (Jakobsen 2014a).

To assess the potential impact of missing SDs for continuous outcomes, we planned to perform the following sensitivity analyses: where SDs were missing and it was not possible to calculate them, we planned to impute SDs from trials with similar populations and low risk of bias. If there were no such trials, we would impute SDs from trials with a similar population. As the final option, we planned to impute SDs from all trials.

1. To assess the potential impact of meta-analysing trials comparing two low targets (FiO_2 below 0.5 or PaO_2 below 10 kPa or SaO_2/SpO_2 below 95%) or two high targets (FiO_2 above 0.5 or PaO_2 above 10 kPa or SaO_2/SpO_2 above 95%), we performed sensitivity analysis excluding trials comparing two low targets or two high targets.
2. To assess the impact of longer follow-up, we performed analyses at maximum follow-up.

'Summary of findings' tables and GRADE

We used the GRADE system to assess the certainty of the body of evidence associated with each of the primary outcomes (all-cause mortality, proportion of participants with one or more serious adverse events, quality of life) and secondary outcomes (lung injury, acute myocardial infarction, stroke, sepsis) by constructing Summary of findings for the main comparison (Guyatt 2008), employing GRADEpro GDT software (GRADEpro GDT). For each primary and secondary outcome, we planned first to present summaries of findings in RCTs with an overall low risk of bias, and second results in all trials.

The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The measure of a body of evidence considers within-study risk of bias, directness of the evidence, heterogeneity of the data, precision of effect estimates (Jakobsen 2014a), and risk of publication bias. We did not expect to identify any trials using adequate blinding of participants and personnel due to the practice of administration of oxygen. Hence, we planned to base our primary conclusions on the results of the analyses of the primary outcomes with low risk of bias in all 'Risk of bias' domains except 'blinding of participants and personnel'.

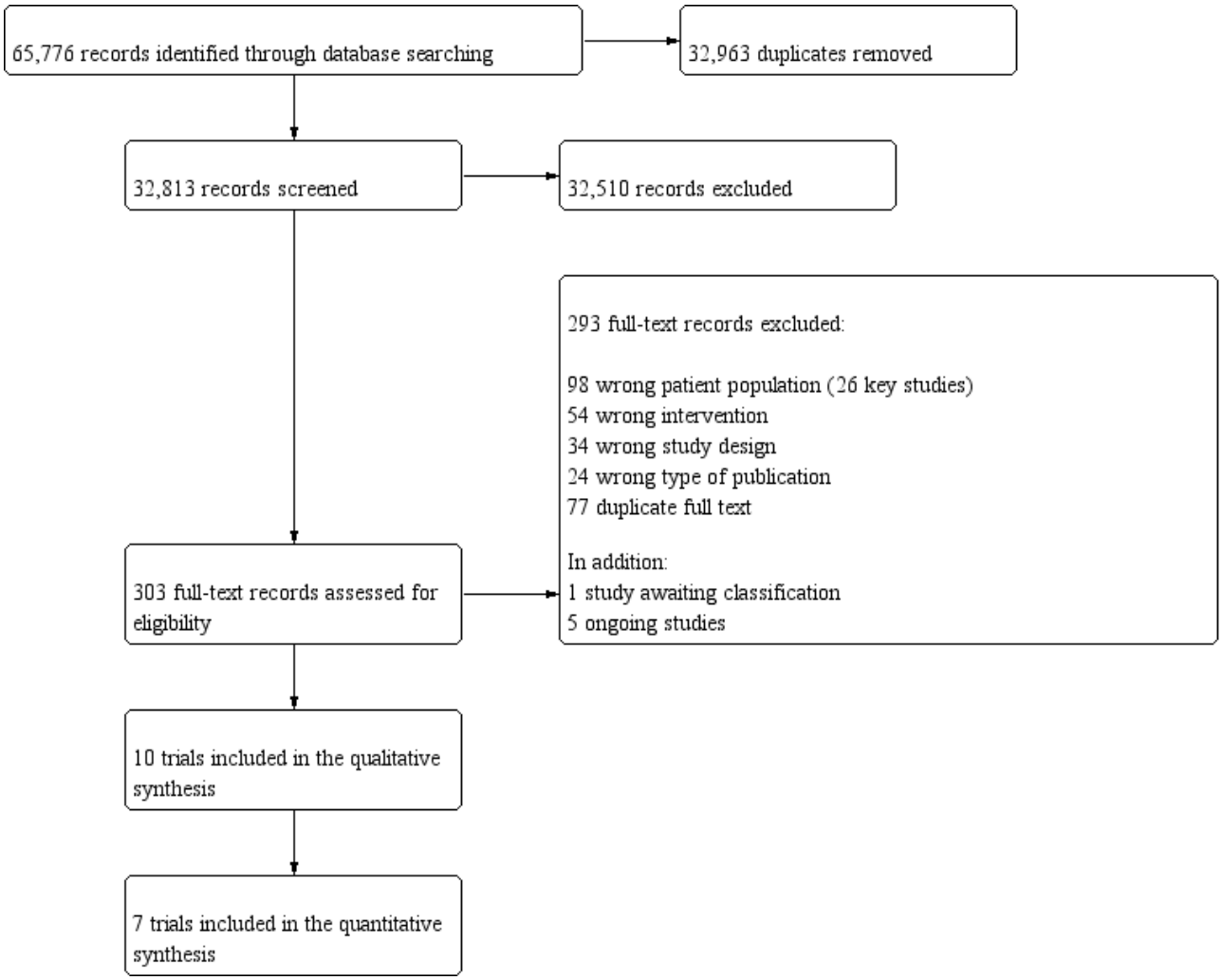
RESULTS

Description of studies

Results of the search

We screened 32,813 titles and abstracts, which included forward and backward citation searches, clinical trials registers, and grey literature. We obtained 303 full-text reports to assess eligibility (Figure 1) and excluded 293 references (98 wrong population, 54 wrong intervention, 34 wrong study design, 24 wrong type of publication, 77 duplicate full text, 5 ongoing studies, and 1 study awaiting classification) from the meta-analyses.

Figure 1. Study flow diagram.



Ten RCTs including a total of 1458 participants fulfilled our inclusion criteria. We approached all 10 corresponding authors to request missing or unclear information and received a reply from six. Detailed descriptions are shown in the Characteristics of included studies table.

See Figure 1.

Included studies

We included 10 RCTs involving a total of 1458 participants randomly assigned to a higher versus lower fraction of inspired oxygen or targets of arterial oxygenation. Seven trials reported on outcomes for this review (Characteristics of included studies).

Trial characteristics

Seven trials reported on mortality (1285 participants) (Asfar 2017; Girardis 2016; Gomersall 2002; Jakkula 2018; Lång 2018; Mazdeh 2015; Panwar 2016).

The same seven trials reported on the proportion of participants with one or more serious adverse events or any serious adverse event (1285 participants).

Five trials reported on lung injury (1167 participants) (Asfar 2017; Girardis 2016; Jakkula 2018; Lång 2018; Panwar 2016), and one trial reported on sepsis (445 participants) (Girardis 2016). Three trials did not report on any of our outcomes (Ishii 2018; Taher 2016; Young 2017). Eight trials used a two-arm, parallel-group design, and two trials used a two-factorial design. The trials were published from 2002 to 2018. Five trials were conducted in Europe; two in Iran; one in New Zealand; one in Australia, New Zealand, and France; and one in Japan.

See Characteristics of included studies.

Participants

The number of participants in the trials ranged from 36 to 480. The approximate weighted mean age of participants was 61 years, and the approximate mean proportion of men was 64%.

All trials included adults admitted to the ICU. Five trials included adults admitted to a multidisciplinary ICU (Asfar 2017; Girardis 2016; Gomersall 2002; Panwar 2016; Young 2017), and one to a surgical ICU (Ishii 2018). Two trials included adults with traumatic brain injury (Lång 2018; Taher 2016); one trial adults after cardiac arrest and resuscitation (Jakkula 2018); and one trial adults

with stroke (Mazdeh 2015). Six trials included adults receiving invasive mechanical ventilation; three trials adults receiving any non-invasive oxygen administration; and one trial both adults on invasive mechanical ventilation and adults receiving non-invasive oxygen administration.

Funding

Seven trials were funded by public grants (Asfar 2017; Girardis 2016; Gomersall 2002; Lång 2018; Mazdeh 2015; Panwar 2016; Taher 2016; Young 2017); one trial did not report how it was funded (Ishii 2018); and one trial was funded by public and private funds and specified that funding bodies had no input regarding the design, management, or reporting of the trial (Jakkula 2018).

Experimental intervention

Of the 10 included trials, four trials randomized participants to higher versus lower oxygen using FiO_2 (Ishii 2018; Lång 2018; Mazdeh 2015; Taher 2016); five trials randomized participants to an oxygenation target (Girardis 2016; Gomersall 2002; Jakkula 2018; Panwar 2016; Young 2017); and one trial randomized participants to a specific FiO_2 in the experimental group and to target an oxygen saturation in the control group (Table 1) (Asfar 2017).

Of the five trials using FiO_2 in the experimental group, two trials used a FiO_2 of 1.0 (Asfar 2017; Ishii 2018); one used FiO_2 of 0.80 (Taher 2016); one used FiO_2 of 0.70 (Lång 2018); and one trial used FiO_2 of 0.50 (Mazdeh 2015). Of the five trials aiming to reach a target in the experimental group, one trial targeted an SpO_2 of 97% to 100% (Girardis 2016); one trial targeted an SpO_2 of ≥ 96% (Panwar 2016); one trial targeted a PaO_2 above 9.0 kPa (67.5 mmHg) (Gomersall 2002); one trial targeted 20 to 25 kPa (150 to 187.5 mmHg) (Jakkula 2018); and one trial randomized participants to standard care (no specific measures taken to avoid high FiO_2 or SpO_2; however, FiO_2< 0.30 was discouraged) (Young 2017).

Two trials were categorized as using a low target in the experimental (higher) group (Gomersall 2002; Mazdeh 2015), and seven trials were categorized as using a high target in the experimental group (Asfar 2017; Girardis 2016; Ishii 2018; Jakkula 2018; Lång 2018; Panwar 2016; Taher 2016). One trial could not be categorized according to our definitions, as no specific target was used (Young 2017).

Comparator intervention

Three trials used FiO_2 in the control group; one trial used expected FiO_2 to achieve a PaO_2 of 100 mmHg (13.3 kPa) (Ishii 2018); one trial used FiO_2 of 0.40 (Lång 2018); and one trial used FiO_2 of 0.50 (Table 1) (Taher 2016). Six trials used a target in the control group: one trial used SpO_2 88% to 92% (Panwar 2016); one trial used SaO_2 between 88% and 95% (Asfar 2017); one trial used SpO_2 between 94% and 98% (Girardis 2016); one trial used PaO_2 of > 6.6 kPa (50 mmHg) (Gomersall 2002); one trial used SpO_2 between 95% and 98% (Jakkula 2018); and one trial used SaO_2/SpO_2 between 91% to 96% (Young 2017). One trial used no supplemental oxygen (Mazdeh 2015).

Six trials were categorized as using a low target in the control group (Asfar 2017; Gomersall 2002; Mazdeh 2015; Panwar 2016; Taher 2016; Young 2017), and four trials were categorized as using a high target in the control group (Girardis 2016; Ishii 2018; Jakkula 2018; Lång 2018).

Excluded studies

We excluded RCTs of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation that were conducted in populations not being admitted to an ICU. We listed the reasons for exclusion of 26 key excluded studies, which included RCTs of higher versus lower oxygen tensions for participants who were critically ill but not admitted to the ICU, as detailed in the Characteristics of excluded studies table.

Awaiting classification

One trial is awaiting classification (ICU-ROX 2019). This study was ongoing at the time of the search and will be included in future updates of this review. See Characteristics of studies awaiting classification.

Ongoing studies

We identified five ongoing trials (NCT02321072; NCT02713451; NCT03141099; NCT03174002; NCT03287466), which we will include in future updates of this review. See Characteristics of ongoing studies.

Risk of bias in included studies

Two trials had low risk of bias in all domains, except for blinding of participants and personnel. The remaining eight trials had high or unclear risk of bias in one or more bias domains other than blinding of participants and personnel. See the 'Risk of bias' graph (Figure 2) and 'Risk of bias' summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

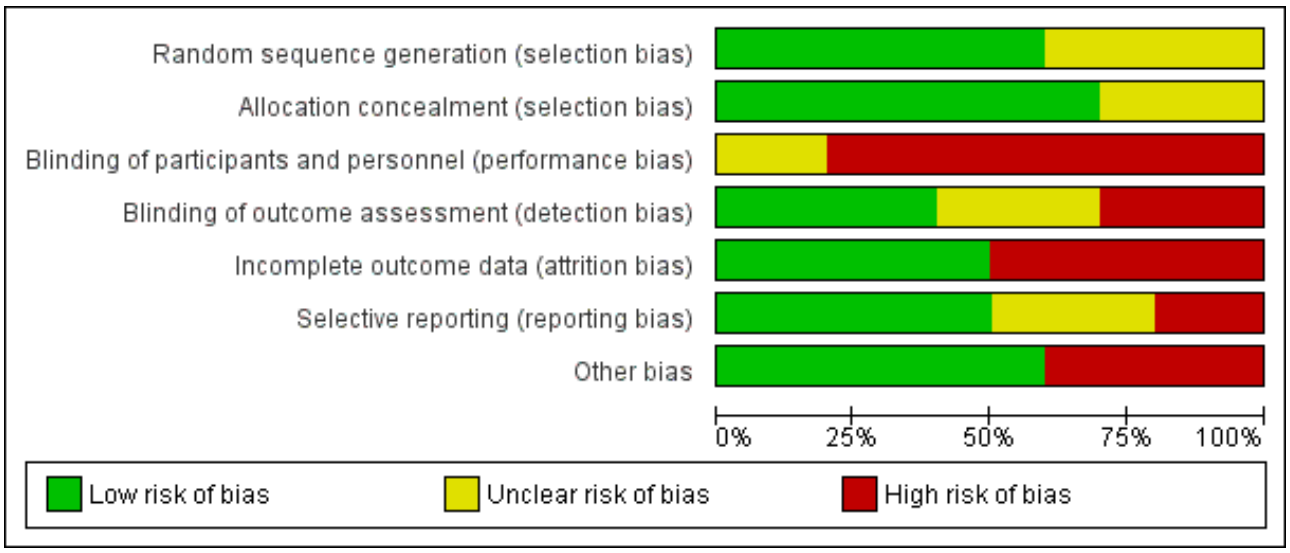
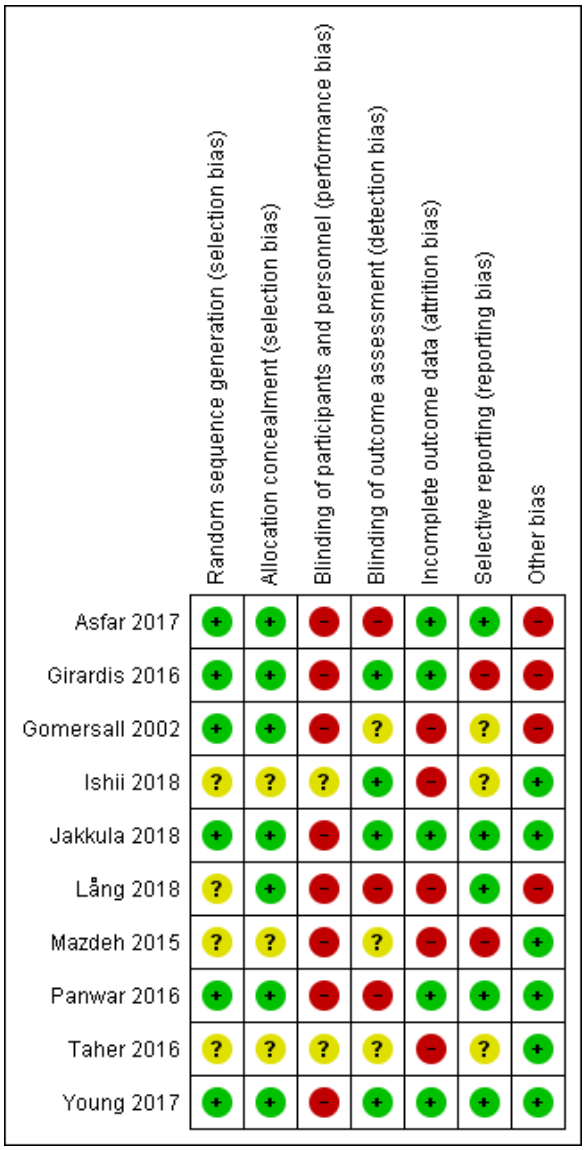


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generation of the allocation sequence

Six trials described generation of the allocation sequence adequately, using computer-generated random numbers. Four trials did not describe the method of sequence generation and were considered to have an unclear risk of bias.

Allocation concealment

Seven trials described adequate allocation concealment, whilst three trials did not describe whether allocation concealment was adequate and were thus judged as having an unclear risk of bias.

Blinding

Blinding of participants and personnel

We judged no trials as having a low risk of bias for blinding of participants and personnel. Three trials blinded participants; five trials did not blind participants and personnel to the interventions; and two trials did not describe whether participants and personnel were blinded to the intervention and were thus judged as having an unclear risk of bias.

Blinding of outcome assessors

Four trials described adequate blinding of outcome assessors; three trials did not describe blinding of outcome assessors and were thus judged as at unclear risk of bias; and three trials used non-blinded outcome assessors.

Incomplete outcome data

Five trials provided numbers and reasons for dropouts and withdrawals or reported no dropouts or withdrawals, whilst five trials were judged as at high risk of bias due either to a high number of dropouts or lost to follow-up, dropouts and participants lost to follow-up not specified by allocation group, or participants being excluded due to mortality or lost to follow-up.

Selective reporting

Five trials were registered before randomization and reported on predefined outcomes; three trials provided insufficient information to determine if they had registered their trial or published a protocol before randomization; and two trials were judged as at high risk of bias due to being registered retrospectively.

Seven trials reported on all-cause mortality; one trial reported on proportion of participants with one or more serious adverse events, and seven trials reported on individual serious adverse events; no trials reported on quality of life; no trials reported on proportion of participants with lung injury, but five trials reported on either ARDS or pneumonia; no trials reported on acute myocardial infarction or stroke; and one trial reported on sepsis.

Other potential sources of bias

We assessed three trials as at high risk of bias due to early stopping: one trial was stopped after a pre-planned interim analysis for a reason that was not prespecified; one trial was stopped after an interim analysis that was not pre-planned; and one trial was stopped early due to lack of funding and slow recruitment.

We judged one trial as at high risk of bias due to a difference in co-interventions between groups, in which the participants in the low-oxygen tension group also received doxapram if they developed an acidosis with pH < 7.2, whereas those in the high-oxygen tension group received doxapram if they developed symptomatic acidosis.

We assessed two trials as at unclear risk of bias for this domain: one trial did not describe funding sources, and one trial was very poorly reported.

Overall risk of bias

We judged all included trials as at overall high risk of bias. Our assessment of risk of bias of the published trial reports is shown in Figure 2 and Figure 3 (Characteristics of included studies).

Effects of interventions

See: **Summary of findings for the main comparison** Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU

See Summary of findings for the main comparison

Primary outcomes

All-cause mortality

Time point closest to three months

Four of 10 trials with a total of 1135 participants and a mean follow-up of 2 months (range 1 to 3 months) reported on all-cause mortality (Asfar 2017; Girardis 2016; Jakkula 2018; Panwar 2016).

A total of 39.1% in the higher group versus 33.1% in the lower group died. Meta-analysis showed evidence of a harmful effect of higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing mortality (random-effects model risk ratio (RR) 1.18, 95% confidence interval (CI) 1.01 to 1.37; $I^2 = 0\%$; 1135 participants; 4 trials; Analysis 1.1; very low-certainty evidence).

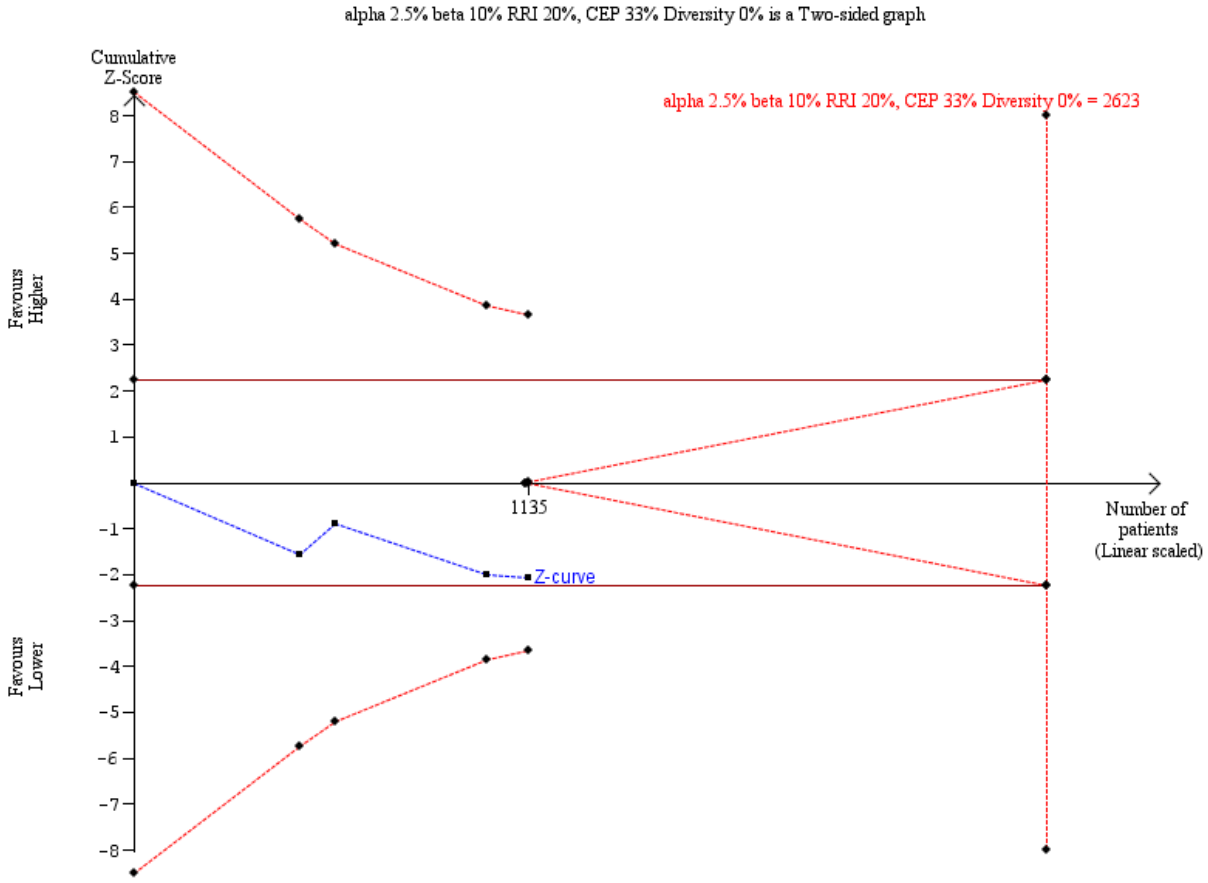
Heterogeneity

Neither visual inspection of the forest plot nor inconsistency factor (I^2 = 0%; 95% CI 0.00 to 0.59; P = 0.63) indicated statistical heterogeneity.

Trial Sequential Analysis

Trial Sequential Analysis showed that with an anticipated RRI of 20%, mortality in the control group of 33%, a type 1 error of 2.5%, a type 2 error of 10%, and a diversity of 0%, the required information size was 2623 participants. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility. This indicated that considering sparse data and repetitive testing, evidence was insufficient to confirm or refute a 20% RRI of higher versus lower oxygen (Figure 4). The TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing, for the intervention effect was 0.88 to 1.57.

Figure 4. Trial Sequential Analysis of the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the risk of mortality at the time point closest to three months. The analysis was based on a control event proportion (CEP) of 33%, a relative risk increase (RRI) of 20%, a type 1 error (alpha) of 2.5%, a type 2 error (beta) of 10%, and a diversity of 0%. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility.



Bayes factor

Bayes factors are presented in Table 2.

Sensitivity analyses

We were unable to perform the sensitivity analysis excluding trials at overall high risk of bias (except for blinding of participants and personnel) as only one trial reporting on mortality was at overall low risk of bias (except for blinding of participants and personnel) (Jakkula 2018).

The sensitivity analysis excluding trials comparing two low targets or two high targets indicated no evidence of a difference in the effect of higher versus lower oxygen on all-cause mortality (RR 1.11, 95% CI 0.92 to 1.35; I^2 = 0%; 537 participants; 2 trials; Analysis 1.2).

The sensitivity analysis based on missing data indicated that incomplete outcome data alone had the potential to influence the results:

- best-worst-case scenario random-effects meta-analysis: RR 1.13, 95% CI 0.97 to 1.31; 1149 participants; 4 trials; Analysis 1.3;
- worst-best-case scenario random-effects meta-analysis: RR 1.21, 95% CI 1.04 to 1.41; 1149 participants; 4 trials; Analysis 1.4).

However, both sensitivity analyses indicated harm of higher versus lower oxygen supplementation. Data were imputed for four trials (Asfar 2017; Girardis 2016; Jakkula 2018; Panwar 2016).

Subgroup analyses

We found no evidence of a difference in subgroup analyses according to different types of oxygen interventions (Analysis 1.5); FiO_2 or oxygenation target in the higher oxygen-administration group (analysis not applicable; Analysis 1.6); FiO_2 or oxygenation target in the lower oxygen-administration group (Analysis 1.7); ICU population (Analysis 1.8); and oxygen delivery system (Analysis 1.9).

Maximum follow-up

Seven of 10 trials with a total of 1285 participants and a mean follow-up of 3.33 months (range 1 month to 6 months) reported all-cause mortality. A total of 36.41% in the higher group versus 31.39% in the lower group died. Meta-analysis showed evidence of a harmful effect of higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation

when assessing mortality (random-effects model RR 1.16, 95% CI 1.00 to 1.35; I^2 = 0%; 1285 participants; 7 trials; Analysis 2.1; very low-certainty evidence).

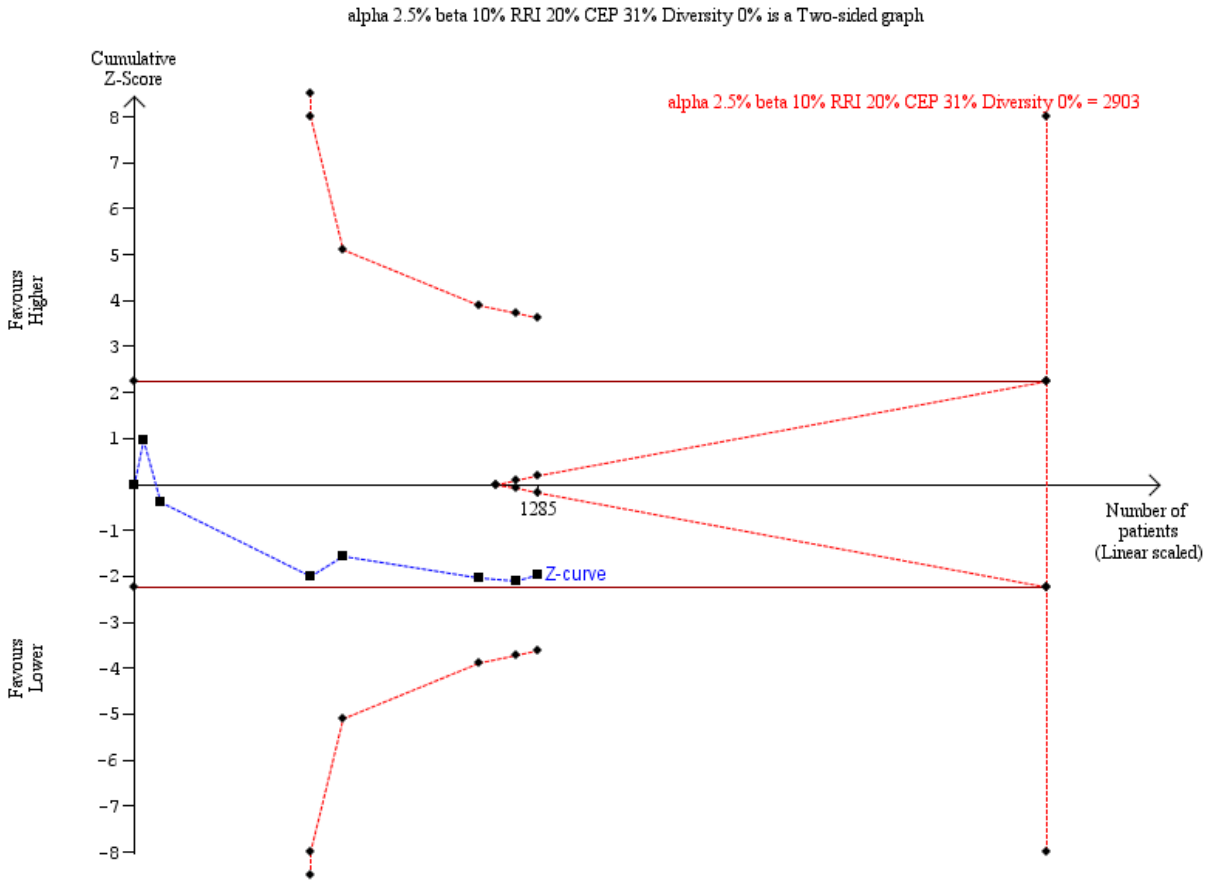
Heterogeneity

Neither visual inspection of the forest plot nor inconsistency factor (I^2 = 0%; 95% CI 0.00 to 0.46; P = 0.76) indicated any heterogeneity.

Trial Sequential Analysis

Trial Sequential Analysis showed that with an anticipated RRI of 20%, mortality in the control group of 31%, a type 1 error of 2.5%, a type 2 error of 10%, and a diversity of 0%, the required information size was 2903 participants. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility. This indicated that considering sparse data and repetitive testing, evidence was insufficient to confirm or refute a 20% RRI of higher versus lower oxygen (Figure 5). The TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing, for the intervention effect was 0.88 to 1.53.

Figure 5. Trial Sequential Analysis of the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the risk of mortality at maximum follow-up. The analysis was based on a control event proportion (CEP) of 31%, a relative risk increase (RRI) of 20%, a type 1 error (alpha) of 2.5%, a type 2 error (beta) of 10%, and a diversity of 0%. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility.



Bayes factor

Bayes factors are presented in Table 2.

Sensitivity analyses

We were unable to perform the sensitivity analysis excluding trials at overall high risk of bias (except for blinding of participants and personnel) as only one trial reporting on mortality was at overall low risk of bias (except for blinding of participants and personnel) (Jakkula 2018).

The sensitivity analysis excluding trials comparing two low targets or two high targets indicated a harmful effect of higher versus lower oxygen on all-cause mortality (RR 1.11, 95% CI 0.92 to 1.35; I^2 = 0%; 537 participants; 2 trials; Analysis 2.2).

The sensitivity analysis on missing data indicated that incomplete outcome data alone had the potential to influence the results:

- best-worst-case scenario random-effects meta-analysis: RR 1.11, 95% CI 0.96 to 1.28; 1306 participants; 7 trials; Analysis 2.3;

- worst-best-case scenario random-effects meta-analysis: RR 1.21, 95% CI 1.05 to 1.41; 1306 participants, 7 trials; Analysis 2.4.

However, both analyses indicated harm of higher versus lower oxygen supplementation. Data were imputed for six trials (Asfar 2017; Girardis 2016; Gomersall 2002; Jakkula 2018; Lång 2018; Panwar 2016).

Subgroup analyses

We found no evidence of a difference in subgroup analyses according to different types of oxygen interventions (Analysis 2.5); FiO_2 or oxygenation/target in the higher oxygen-administration group (Analysis 2.6); FiO_2 or oxygenation/target in the lower oxygen-administration group (Analysis 2.7); ICU population (Analysis 2.8); and oxygen delivery system (Analysis 2.9).

Proportion of participants with one or more serious adverse events

One of 10 trials reported on the proportion of participants with one or more serious adverse events as a composite outcome, according to our primary analysis on the proportion of participants with one or more serious adverse events (Asfar 2017). A total of 85% in the higher group versus 76% in the lower group had at least one serious adverse event. Another six trials, Girardis 2016; Gomersall 2002; Jakkula 2018; Lång 2018; Mazdeh 2015; Panwar 2016, reported on outcomes categorized by us as serious adverse events according to the ICH-GCP definition (ICH-GCP 1997).

As the reporting of serious adverse events as a combined outcome was not carried out according to the ICH-GCP recommendation, we estimated the reported proportion of participants with one or more serious adverse events in two ways:

1. by choosing the one specific serious adverse event with the highest proportion reported in each trial that addresses the lowest possible proportion of participants with one or more serious adverse events (somehow a best-case scenario);
2. by cumulating all reported serious adverse events, assuming that participants only experience one serious adverse event (the number of participants in each group will constitute a maximum), address the highest possible reported proportion of participants with one or more serious adverse events (somehow a worst-case scenario).

Time point closest to three months (follow-up range 3 days to 90 days)

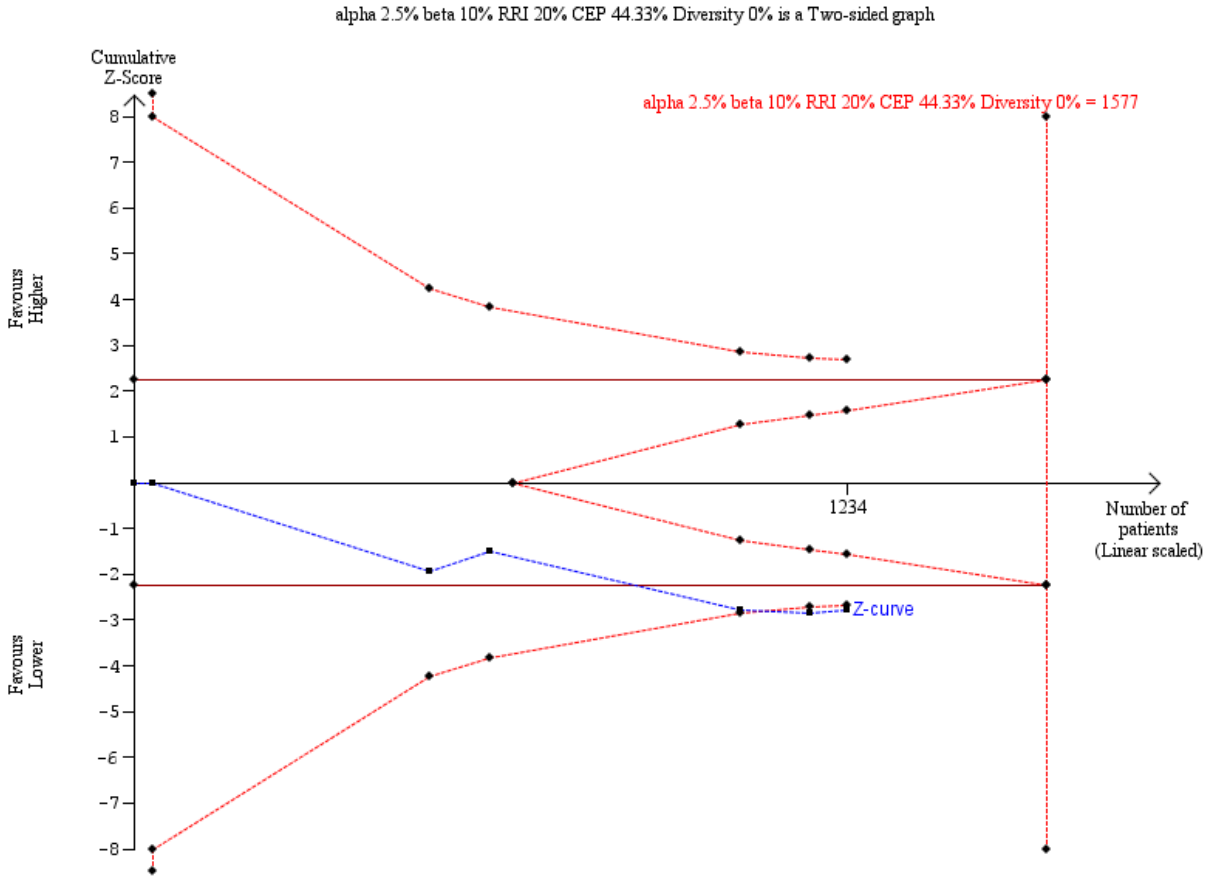
Meta-analysis showed evidence of a harmful effect of higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing the estimated highest reported proportion of specific serious adverse events in each trial (random-effects model RR 1.13, 95% CI 1.04 to 1.23; I^2 = 0%; 1234 participants; 6 trials; Analysis 3.1; very low-certainty evidence). Individual types of serious adverse events included mortality (Girardis 2016; Jakkula 2018; Panwar 2016); proportion of participants with one or more serious adverse events (Asfar 2017); mechanical ventilation (reported as a poor outcome) (Gomersall 2002); and pneumonia (Lång 2018).

Meta-analysis showed no evidence of a difference of higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing the estimated cumulated number of serious adverse events (random-effects model RR 1.08, 95% CI 0.99 to 1.18; I^2 = 49%; 1234 participants; 6 trials; Analysis 3.2; very low-certainty evidence). Individual types of serious adverse events included mortality; ARDS; pneumonia; sepsis; respiratory failure; cardiovascular failure; liver failure; renal failure; bloodstream infection; respiratory infection; surgical site infection; peripheral arterial thrombosis, pneumothorax; ventricular arrhythmias; new infections (composite outcome: when events were reported individually, they were not included in the analysis); haemodynamic instability; mechanical ventilation; severe hypercapnia and respiratory acidosis ($PaCO_2$ > 10 kPa and pH < 7.15); and unexplained brain oedema on computed tomography (CT) scan.

Trial Sequential Analysis

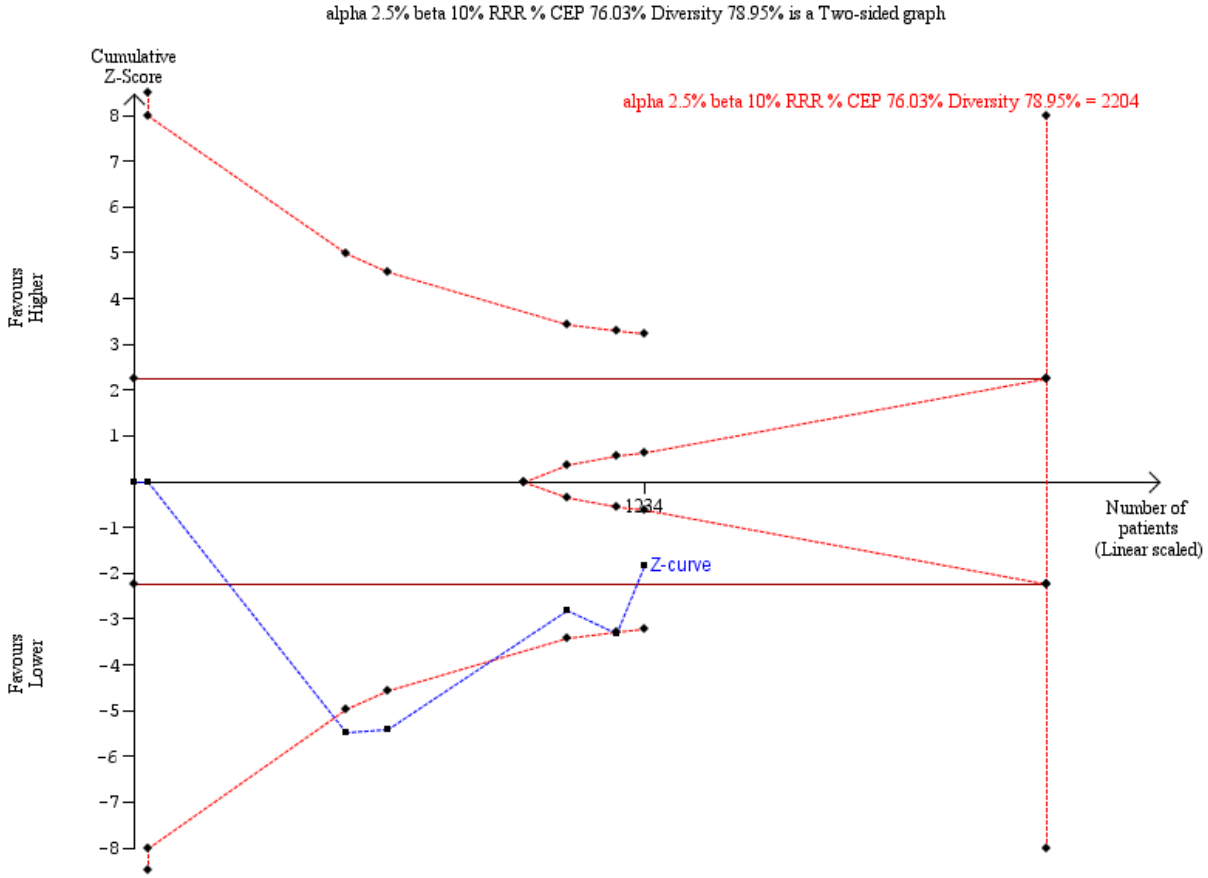
Trial Sequential Analysis of the estimated highest reported proportion of serious adverse events showed that with an anticipated RRI of 20%, serious adverse events in the control group of 44.33%, a type 1 error of 2.5%, a type 2 error of 10%, and a diversity of 0%, the required information size was 1577 participants (Figure 6). The cumulative Z-curve crossed the trial sequential monitoring boundary for harm, indicating there is evidence that higher versus lower oxygen may increase the relative risk of participants with one or more serious adverse events at three months follow-up. The TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing, for the intervention effect was 1.00 to 1.27.

Figure 6. Trial Sequential Analysis of the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the risk of the estimated highest reported proportion of serious adverse events at the time point closest to three months. The analysis was based on a control event proportion (CEP) of 44.33%, a relative risk increase (RRI) of 20%, a type 1 error (alpha) of 2.5%, a type 2 error (beta) of 10% and a diversity of 0%. The cumulative Z-curve crossed the trial sequential monitory boundary for harm.



Trial Sequential Analysis of the estimated cumulated number of serious adverse events showed that with an anticipated RRR of 20%, serious adverse events in the control group of 76.03%, a type 1 error of 2.5%, a type 2 error of 10%, and a diversity of 78.95%, the required information size was 2204 (Figure 7). The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility (although reaching futility boundary). This indicated that considering sparse data and repetitive testing, evidence was insufficient to confirm or refute a 20% RRR of higher versus lower oxygen. The TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing, for the intervention effect was 0.94 to 1.25.

Figure 7. Trial Sequential Analysis of the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the risk of the estimated cumulated proportion of serious adverse events at time point closest to three months. The analysis was based on a control event proportion (CEP) of 76.03%, a relative risk reduction (RRR) of 20%, a type 1 error (alpha) of 2.5%, a type 2 error (beta) of 10%, and a diversity of 78.95%. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility.



Bayes factor

Bayes factors are presented in Table 2.

Maximum follow-up (follow-up range 6 days to 6 months)

Meta-analysis showed evidence of a harmful effect of higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing the estimated highest reported proportion of serious adverse events (random-effects model RR 1.13, 95% CI 1.04 to 1.23; $I^2 = 0\%$; 1285 participants; 7 trials; Analysis 4.1). Individual types of serious adverse events included mortality (Girardis 2016; Jakkula 2018; Lång 2018; Mazdeh 2015; Panwar 2016); proportion of participants with one or more serious adverse events (Asfar 2017); and mechanical ventilation (Gomersall 2002).

Meta-analysis showed no evidence of a difference between higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing the estimated cumulated number of serious adverse events (random-effects model RR 1.07, 95% CI 0.97 to 1.18; I^2 = 49%; 1285 participants; 7 trials; Analysis 4.2). Individual types of serious adverse events included mortality; ARDS; pneumonia; sepsis; respiratory failure; cardiovascular failure; liver failure; renal failure; bloodstream infection; respiratory infection; surgical site infection; peripheral arterial thrombosis, pneumothorax; ventricular arrhythmias; new infections (composite outcome: when events were reported individually, they were not included in the analysis); cardiac arrhythmia; coma; haemodynamic instability; mechanical ventilation; severe hypercapnia and respiratory acidosis ($PaCO_2$ > 10 kPa and pH < 7.15); and unexplained brain oedema on CT scan.

Trial Sequential Analysis

Trial Sequential Analysis of the estimated highest reported proportion of serious adverse events showed that with an anticipated RRI of 20%, serious adverse events in the control group of 43.38%, a type 1 error of 2.5%, a type 2 error of 10%, and a diversity of 0%, the required information size was 1644 participants. The cumulative Z-curve crossed the trial sequential monitoring boundary for harm. This indicated that there was firm evidence that higher versus lower oxygen increases serious adverse events at maximum follow-up. The TSA CI, adjusted for multiple outcomes,

sparse data, and repetitive testing, for the intervention effect was 1.01 to 1.27.

Trial Sequential Analysis of the estimated cumulated number of serious adverse events showed that with an anticipated RRR of 20%, serious adverse events in the control group of 74.92%, a type 1 error of 2.5%, a type 2 error of 10%, and a diversity of 82.80%, the required information size was 2826 participants. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility (although reaching futility boundary). This indicated that considering sparse data and repetitive testing, evidence was insufficient to confirm or refute a 20% RRI of higher versus lower oxygen. The TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing, for the intervention effect was 0.92 to 3.01.

Bayes factor

Bayes factors are presented in Table 2.

Quality of life (any valid scale such as the 36-item Short Form Health Survey (SF-36))

None of the included trials reported any data on quality of life at any time point.

Secondary outcomes

Lung injury

None of the 10 included trials reported any data on lung injury (as a composite outcome defined as either ARDS, pulmonary fibrosis, or pneumonia) at any time point. Five of the 10 trials reported on specific lung outcomes: ARDS (Jakkula 2018; Lång 2018; Panwar 2016); pulmonary fibrosis not reported; pneumonia (Asfar 2017; Girardis 2016; Lång 2018), during index admission.

We estimated the reported proportion of participants with one or more lung injury in two ways:

1. by choosing the one specific lung injury event with the highest proportion reported in each trial that addresses the lowest possible proportion of participants with one or more lung injuries (somehow a best-case scenario);
2. by cumulating all reported lung injury events, assuming that participants only experience one lung injury event (the number of participants in each group will constitute a maximum), address the highest possible reported proportion of participants with one or more lung injuries (somehow a worst-case scenario).

Time point closest to three months (follow-up range median 4 days to median 23 days)

Meta-analysis showed no evidence of a difference between higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing the estimated highest reported proportion of lung injury (fixed-effect model RR 1.03, 95% CI 0.78 to 1.36; I^2 = 0%; 1167 participants; 5 trials; Analysis 5.1; very low-certainty evidence).

Meta-analysis showed no evidence of a difference between higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing the estimated cumulated number of lung injury events (fixed-effect model RR 0.99, 95% CI 0.75 to 1.30; I^2 = 0%; 1167 participants; 5 trials; Analysis 5.2; very low-certainty evidence).

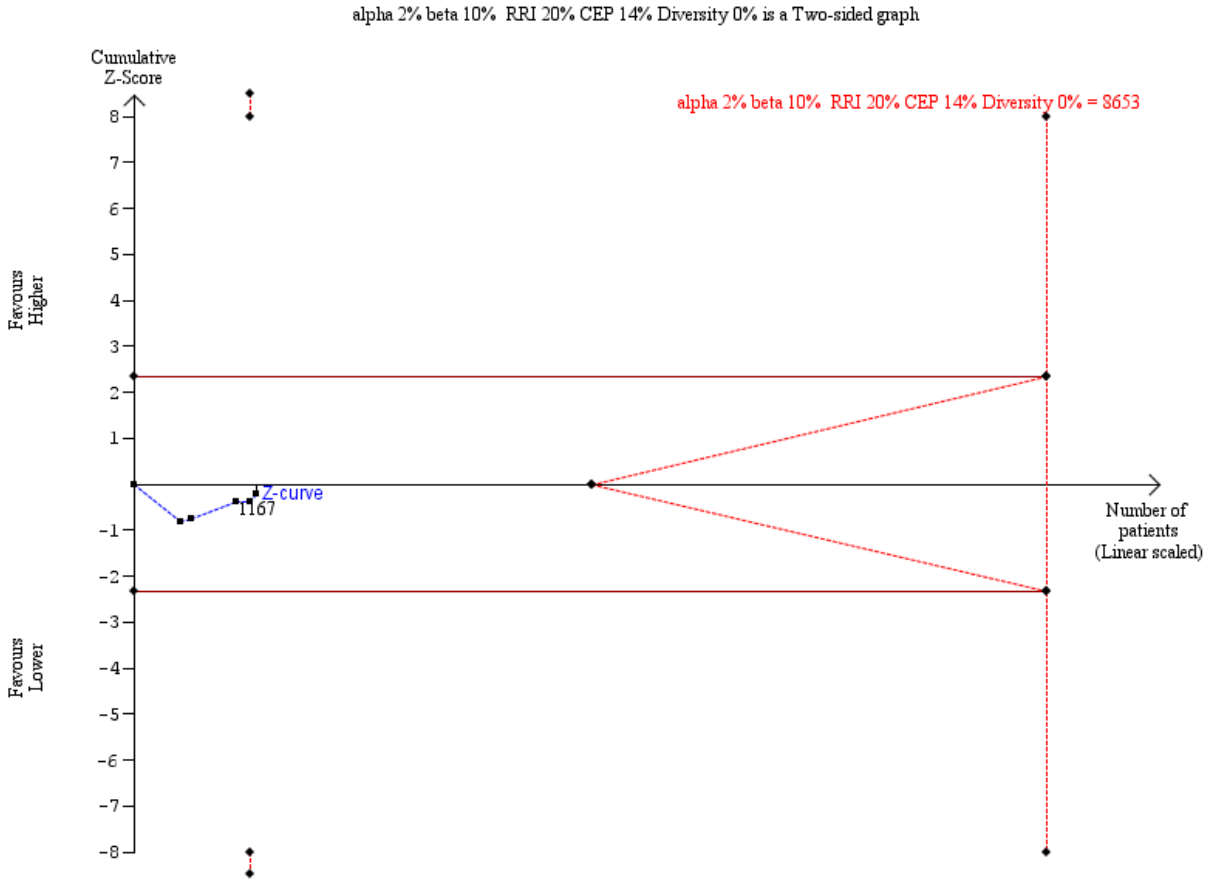
Three of 10 trials with a total of 288 participants reported ARDS. A total of 10.7% in the lower group versus 8.1% in the higher group had ARDS. Meta-analysis showed no evidence of a difference between higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing ARDS (random-effects model RR 0.79, 95% CI 0.28 to 2.20; I^2 = 16%; 288 participants; 3 trials; Analysis 5.3; very low-certainty evidence).

Three of 10 trials with a total of 944 participants reported pneumonia. A total of 14.7% in the lower group versus 15.2% in the higher group had pneumonia. Meta-analysis showed no evidence of a difference between higher fraction of inspired oxygen or targets compared with lower fraction or targets of arterial oxygenation when assessing pneumonia (fixed-effect model RR 1.03, 95% CI 0.76 to 1.40; I^2 = 0%; 944 participants; 3 trials; Analysis 5.4; very low-certainty evidence).

Trial Sequential Analysis

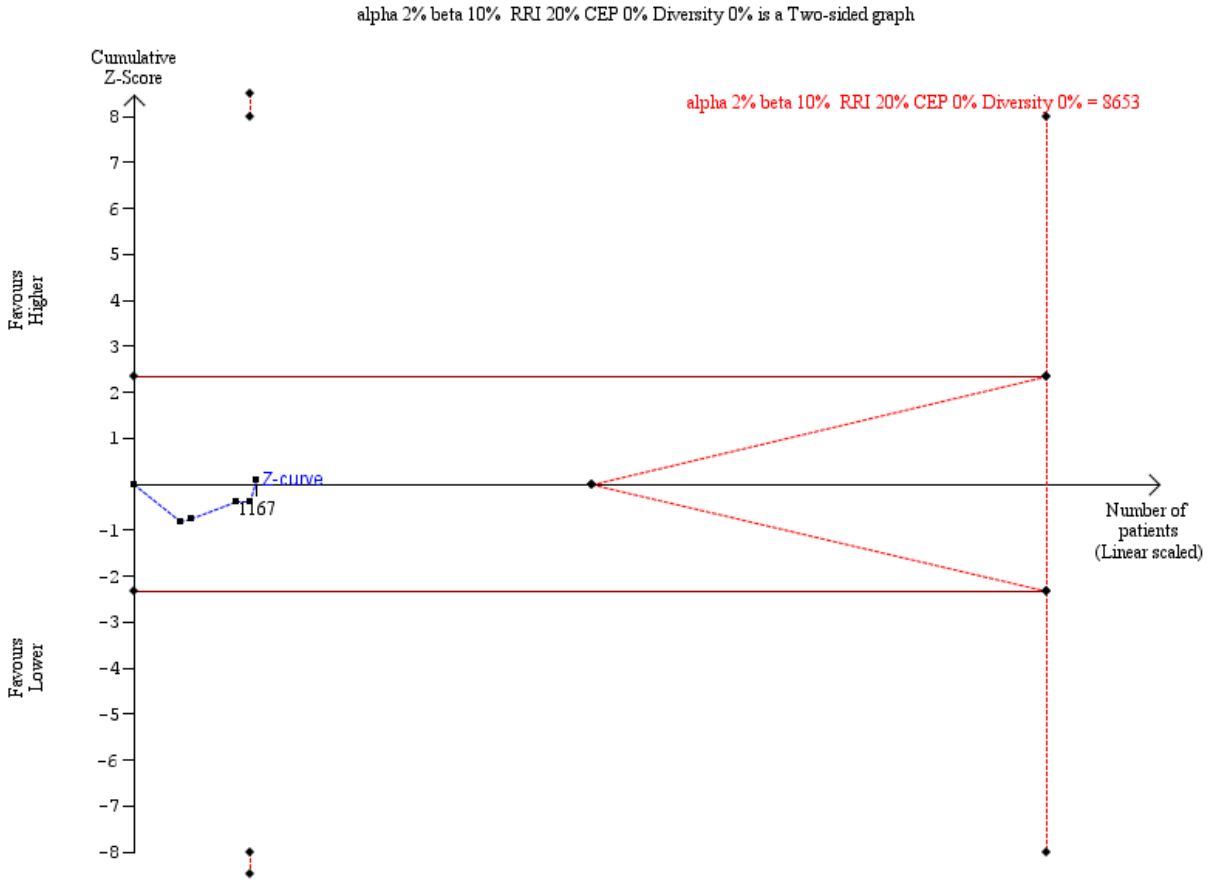
Trial Sequential Analysis of the estimated highest reported proportion of lung injuries showed that with an anticipated RRI of 20%, lung injury in the control group of 14%, a type 1 error of 2%, a type 2 error of 10%, and a diversity of 0%, the required information size was 8653 participants (Figure 8). The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility. This indicated that considering sparse data and repetitive testing, evidence was insufficient to confirm or refute a 20% RRR or 20% RRI for benefit or harm of higher versus lower oxygen. The TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing, for the intervention effect was 0.33 to 3.23.

Figure 8. Trial Sequential Analysis of the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the risk of the estimated highest reported proportion of lung injury at the time point closest to three months. The analysis was based on a control event proportion (CEP) of 14%, a relative risk increase (RRI) of 20%, a type 1 error (alpha) of 2%, a type 2 error (beta) of 10%, and a diversity of 0%. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility.



Trial Sequential Analysis of the estimated cumulated number of lung injuries showed that with an anticipated RRI of 20%, lung injury in the control group of 14%, a type 1 error of 2%, a type 2 error of 10%, and a diversity of 0%, the required information size was 8653 participants (Figure 9). The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility. This indicated that considering sparse data and repetitive testing, evidence was insufficient to confirm or refute a 20% RRR or 20% RRI for benefit or harm of higher versus lower oxygen. The TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing, for the intervention effect was 0.32 to 3.05.

Figure 9. Trial Sequential Analysis of the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the risk of the estimated cumulated proportion of lung injury at the time point closest to three months. The analysis was based on a control event proportion (CEP) of 14%, a relative risk increase (RRI) of 20%, a type 1 error (alpha) of 2%, a type 2 error (beta) of 10%, and a diversity of 0%. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility.

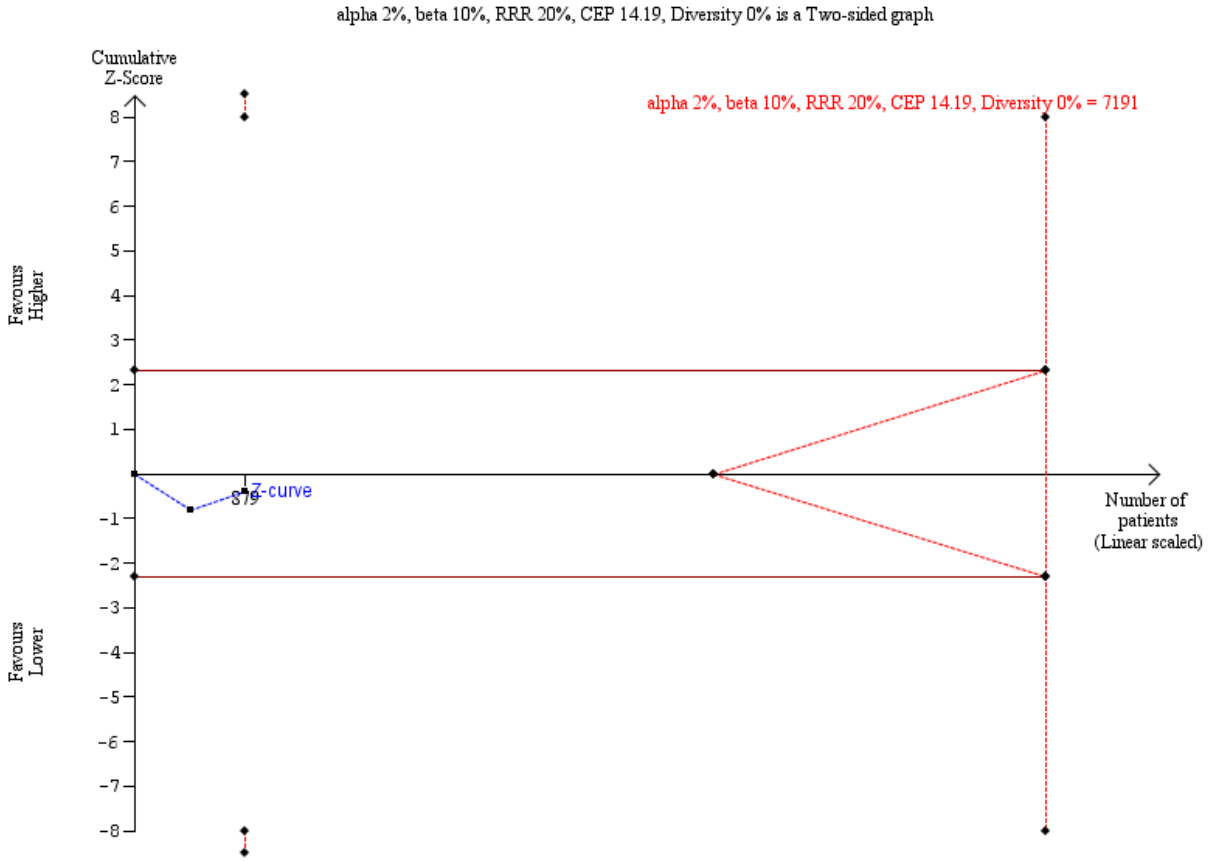


We were unable to conduct Trial Sequential Analysis of ARDS due to insufficient information (1.34%). The required information size was 21,533 participants.

Trial Sequential Analysis of pneumonia showed that with an anticipated RRI of 20%, pneumonia in the control group of 14%, a type 1 error of 2%, a type 2 error of 10%, and a diversity of 0%, the required information size was 10,200 participants (Figure 10).

The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility. This indicated that considering sparse data and repetitive testing, evidence was insufficient to confirm or refute a 20% RRR or 20% RRI for benefit or harm of higher versus lower oxygen. The TSA CI, adjusted for multiple outcomes, sparse data, and repetitive testing, for the intervention effect was 0.30 to 3.57.

Figure 10. Trial Sequential Analysis of the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the risk of pneumonia at the time point closest to three months. The analysis was based on a control event proportion (CEP) of 14%, a relative risk reduction (RRR) of 20%, a type 1 error (alpha) of 2%, a type 2 error (beta) of 10%, and a diversity of 0%. The cumulative Z-curve did not cross any boundaries for benefit and harm, nor trial sequential monitoring boundaries for futility.



Maximum follow-up

None of the 10 trials reported any data on lung injury (as a composite outcome defined as either ARDS, pulmonary fibrosis, or pneumonia), including specific lung outcomes (ARDS, pulmonary fibrosis, or pneumonia), with longer follow-up than during index admission.

Acute myocardial infarction

None of the included trials reported any data on acute myocardial infarction at any time point.

Stroke

None of the included trials reported any data on stroke at any time point.

Sepsis

One trial reported on sepsis during ICU stay (median 6 days; interquartile range 1 to 11) (Girardis 2016). A total of 9.78% in the higher group versus 5.00% in the lower group had sepsis (RR 1.87, 95% CI 0.93 to 3.87; 1 study; 445 participants; very low-certainty evidence).

DISCUSSION

Summary of main results

We included 10 trials that randomized a total of 1458 participants in this systematic review. Seven trials with a total of 1285 participants contributed data to the analyses. We found no evidence for a beneficial effect of higher versus lower supplemental oxygen for adults admitted to the ICU.

Mortality seems to have been increased with higher supplemental oxygen at the time point closest to three months follow-up (RR 1.18, 95% CI 1.01 to 1.37; 4 studies; 1135 participants; I^2 = 0%; Analysis 1.1; very low-certainty of evidence) (Summary of findings for the main comparison). Trial Sequential Analysis, considering multiple outcomes, sparse data, and repetitive testing, revealed that the information size required to detect or reject an RRI of 20% was not achieved (Figure 11). When mortality was analysed at maximum follow-up, the traditional meta-analysis indicated increased mortality with higher supplemental oxygen (Analysis 2.1), but TSA highlighted that the required information size to detect or reject a 20% RRI in mortality was not achieved (Figure 11).

The estimated highest reported proportion of serious adverse events at the time point closest to three months follow-up was significantly increased with higher supplemental oxygen (RR 1.13, 95% CI 1.04 to 1.23; 6 studies; 1234 participants; I^2 = 0%; Analysis 3.1; very low-certainty evidence). However, the estimated cumulated number of serious adverse events at the time point closest to three months follow-up did not show evidence of a difference (RR 1.08, 95% CI 0.99 to 1.18; 6 studies; 1234 participants; I^2 = 49%; Analysis 3.2; very low-certainty evidence). Trial Sequential Analysis showed that the monitoring boundary for harm for a 20% RRI was crossed when serious adverse events were analysed as the estimated highest proportion (Figure 6). However, when analysed as the estimated cumulated number of serious adverse events, the TSA revealed that the information size required to detect or reject an RRI of 20% was not achieved (Figure 7).

When serious adverse events were analysed at maximum follow-up, the traditional meta-analysis again showed that serious adverse events were increased with higher supplemental oxygen when analysed as the highest proportion (Analysis 4.1), but were not significantly increased when analysed as cumulated events (Analysis 4.2). Trial Sequential Analysis again showed that the monitoring boundary for harm for a 20% RRI was crossed when serious adverse events were analysed as estimated highest proportion, and when analysed as estimated cumulated number of serious adverse events, the TSA again revealed that the information size required to detect or reject an RRI of 20% was not achieved.

There was no evidence of a difference in lung injury with higher supplemental oxygen when analysed as a composite outcome nor as individual components of the composite outcome, but the evidence is very uncertain (Analysis 5.1; Analysis 5.2). However, TSA, considering multiple outcomes, sparse data, and repetitive testing, revealed that only 13% of the required information size was reached to detect or reject a 20% RRI, and that neither conventional nor trial sequential monitoring boundaries for benefit, harm, and futility had been crossed (Figure 8; Figure 9).

Only one trial reported on sepsis. Based on this one trial, we found that sepsis was not affected by higher supplemental oxygen (RR 1.87, 95% CI 0.93 to 3.87; 1 study; 445 participants; very low-certainty evidence).

No trials reported on quality of life, acute myocardial infarction, or stroke.

Overall completeness and applicability of evidence

We included all RCTs up to December 2018 comparing higher to lower oxygen fractions or targets of oxygenation in adults admitted to the ICU.

We found that clinical heterogeneity, especially relating to the intervention, but also to the population and setting, was present. Six trials were conducted in Europe, Australia, and New Zealand (Asfar 2017; Girardis 2016; Jakkula 2018; Lång 2018; Panwar 2016; Young 2017), two in Iran (Mazdeh 2015; Taher 2016), one in Hong Kong (Gomersall 2002), and one in Japan (Ishii 2018). The trials were conducted from 1994, Gomersall 2002, to 2018, Ishii 2018; Young 2017. Mean age spanned from 44 years, Lång 2018, to 68 years, Gomersall 2002, and the percentage of males versus females spanned from 49%, Jakkula 2018, to 84%, Lång 2018. All participants were admitted to the ICU; however, some trials included participants admitted to the ICU regardless of condition, whilst others included specific populations: five trials included adults from multidisciplinary ICUs (Asfar 2017; Girardis 2016; Gomersall 2002 Panwar 2016; Young 2017); two included adults with traumatic brain injury (Lång 2018; Taher 2016); one included adults admitted to a surgical ICU (Ishii 2018); one included adults with acute stroke (Mazdeh 2015); and one included adults resuscitated during out-of-hospital cardiac arrest (Jakkula 2018). In addition, disease severity differed, for example median Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) of 22, Lång 2018, and median APACHE II of 28, Jakkula 2018. Furthermore, the interventions varied to a great extent. The duration of the intervention ranged from one hour, in Ishii 2018, to the entire duration of ICU admission, in Girardis 2016. The intervention targets compared also differed, and only three trials assessed targets categorized by us as higher versus lower oxygen fractions or targets of oxygenation (Asfar 2017; Panwar 2016; Taher 2016).

In general, statistical heterogeneity was low or moderate and was not explained by our subgroup analyses. Our sensitivity analysis on missing data (best-worst-case scenario and worst-best-case scenario) revealed that incomplete outcome data alone had the potential to influence the results on mortality; however, both analyses indicated harm with higher versus lower oxygen supplementation.

Only two trials had low risk of bias in all domains except for blinding of participants and personnel (Jakkula 2018; Young 2017). Only one of these trials contributed data to the meta-analyses (Jakkula 2018). The meta-analyses on mortality and lung injuries did not reach the required information size to detect or reject a 20% RRR or RRI. Trial Sequential Analysis on serious adverse events revealed that the trial sequential monitoring boundary for harm was crossed in one analysis (Figure 6), but not in the other (Figure 7).

Seven trials contributed data to the analyses on mortality and serious adverse events, and five trials contributed data to the analyses on lung injuries. No trials reported on quality of life, acute myocardial infarction, and stroke, and only one trial reported on sepsis.

Quality of the evidence

We used GRADE to assess the certainty of the evidence for the results on all-cause mortality, serious adverse events, quality of life, lung injury, acute myocardial infarction, stroke, and sepsis at the time point closest to three months (Summary of findings for the main comparison).

The GRADE assessment showed that the certainty of evidence was very low for mortality due to serious risk of bias, indirectness, and imprecision.

The certainty of the evidence was very low for the estimated highest reported proportion of serious adverse events due to serious risk of bias, indirectness, and imprecision. Trial Sequential Analysis showed that the trial sequential monitoring boundary for harm was crossed; hence, even with strict control of random errors, disregarding risk of bias, there is evidence that higher versus lower oxygen tensions increases the risk of serious adverse events by at least 20%.

The certainty of the evidence was very low for lung injury due to serious risk of bias, indirectness, and imprecision.

The certainty of the evidence was very low for sepsis due to serious risk of bias, inconsistency, and imprecision.

The certainty of the evidence for quality of life, acute myocardial infarction, and stroke was not estimable due to lack of data.

Potential biases in the review process

Strengths

We included trials regardless of publication type, publication status, language, and choice of outcomes. In all cases we contacted relevant trial authors if additional information was needed.

We used predefined, up-to-date systematic review methodology, and the methodology was not changed during the review process. We used GRADE to assess the certainty of the evidence and TSA as a sensitivity analysis with adjusted thresholds for significance to strictly control the risk of random errors; we thoroughly assessed the risk of bias of each trial to evaluate the risk of systematic errors (bias); and we used an eight-step procedure to assess if the thresholds for statistical and clinical significance were crossed (Jakobsen 2014a). This adds further robustness to our results and conclusions. We also tested the robustness of our results with sensitivity analyses.

We conducted two post hoc analyses that estimated the effects of higher versus lower oxygen supplementation on risk of having one or more serious adverse events and lung injury.

Limitations

We identified a high risk of clinical heterogeneity, especially within the interventions. The most obvious limitation was that trials did not use the same definition of lower targets and higher targets. Some trials used a fixed FiO_2, whilst others used a target interval, and the achieved oxygen saturation may end up being high even though participants were allocated to the lower group. Furthermore, the targets used in some trials were not adequately different to be categorized as trials comparing real high to real low targets. That being said, statistical heterogeneity seemed to be low.

Our 'Risk of bias' assessment showed that none of the included trials had an overall low risk of bias and none were fully blinded, which was not unexpected due to the complexity and difficulties of blinding interventions of oxygen supplementation for participants and personnel. Nevertheless, only data from one trial used blinded outcome assessors, which may still be used when blinding of participants and personnel is not feasible (Pocock 2015). Inadequate blinding is therefore a limitation in the included trials, as it is associated with exaggeration of beneficial intervention effects and underestimation of harmful effects (Hrobjartsson 2014; Savovic 2018). We thus could not rule out a biased effect estimate of the included trials. As a result, we downgraded the certainty of the evidence for all trials one level for risk of bias.

Only one trial reported serious adverse events as a composite outcome of participants with one or more serious adverse events. To estimate the effect on serious adverse events reported in the included trials, we conducted two analyses to estimate the effect on the proportion of participants having one or more serious adverse events, which may be expected to lie between these two extremes. None of the trials reported on lung injuries as a composite outcome, and thus the same method was applied. Each component was analysed separately for the lung injury outcome, but this was not done for serious adverse events. Each component of composite outcomes may not have similar degrees of severity, and therefore could bias the results of the outcome (Garattini 2016). If, for example, more severe serious adverse events occur in one intervention group, and other less severe serious adverse events occur in the other intervention group, then there is a risk of overlooking actual severity differences between the compared groups when analysing the composite outcome.

Furthermore, the analyses estimating the highest proportion of serious adverse events/lung injuries imply that participants included in the highest proportion also include participants having other serious adverse events. For example, if mortality is the highest proportion, then it is implied that all the participants that did not die did not experience another serious adverse event; this analysis thus underestimates the proportion of participants with one or more serious adverse events, as participants not included in the highest proportion would be expected to experience other serious adverse events not included in the highest proportion. In addition, the analyses estimating the cumulated proportion of serious adverse events/lung injuries imply that all participants who experience a serious adverse event had only this specific serious adverse event, which overestimates the proportion of participants with one or more serious adverse events, since a minimum of one participant would be expected to have more than one serious adverse event.

Only seven relatively small trials contributed data to the meta-analyses. An insufficient number of trials precluded an assessment of publication bias. Although we did not observe statistically significant heterogeneity in our subgroup analyses, they were naturally relatively small, thus we cannot exclude the possibility of subgroup differences.

Agreements and disagreements with other studies or reviews

Systematic reviews of observational data have found an association between hyperoxaemia and mortality in critically ill adults (Damiani 2014; Helmerhorst 2015), which has launched the initiation of several RCTs. Some meta-analyses of RCTs have been published in recent years (Cabello 2016; Chu 2018; Sepehrvand 2018; You 2018).

Critical illness of adults in the reviews is often defined differently or represented as subgroups. We included trials assessing adults admitted to and randomized in the ICU, whereas other reviews also included other settings, such as trauma, surgery, or pre-hospital initiated oxygen supplementation. Previous meta-analyses consistently report that too much supplemental oxygen may be/is harmful or not beneficial. However, it appears that none of these meta-analyses included proper bias risk assessment in their conclusions/recommendations. Limitations due to clinical heterogeneity are to a greater or lesser extent highlighted in the reviews, but these also seem not to be reflected in the conclusions. We performed TSA in order to control the risk of random errors in a cumulative meta-analysis and to prevent premature statements regarding the superiority of higher versus lower oxygen supplementation, which was also used by Chu and colleagues but without adjusting for multiple outcomes and using a possible inadequate power of 80% (Chu 2018).

Despite methodological discrepancies between our review and other meta-analyses and reviews, we agree with recently published reviews reporting a possible association between high oxygenation targets and mortality. However, we did not find the available evidence to be of high certainty (Chu 2018). Furthermore, we did not find that the current evidence necessitates a clinical practice guideline recommending a specific target of FiO_2, SpO_2, and PaO_2, particularly due to the very high heterogeneity in the types of interventions in the trials included in this review. (Rasmussen 2018; Siemieniuk 2018).

AUTHORS' CONCLUSIONS

Implications for practice

We are very uncertain about the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit on all-cause mortality, serious adverse events, lung injuries, and sepsis at the time point closest to three months due to very low-certainty evidence. Our results suggest that oxygen supplementation with higher versus lower fractions or oxygenation targets may increase mortality. None of the included trials reported the proportion of participants with one or more serious adverse events according to the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) criteria; however, we found an increase in the number of serious adverse events reported by the trials with higher fractions of inspired oxygen or oxygenation targets using strict control of the risk of random errors. The effects of the interventions on quality of life, acute myocardial infarction, and stroke were inconclusive due to lack of data.

Implications for research

Randomized controlled trials assessing the benefits and harms of higher versus lower oxygen supplementation are needed. Such trials should be conducted with the lowest possible risk of bias, low risk of other design errors, and low risk of random errors. Future trials should focus their assessments on multidisciplinary intensive care units and critically ill adults in general and not only subgroups of this population group (Barbateskovic 2018). Oxygen supplementation is standard care, and the assessed intervention and duration should therefore reflect clinically relevant and accepted supplemental oxygen targets (Schjørring 2018). Furthermore, trials should aim to differentiate the intervention groups so that trials are in fact comparing higher versus lower oxygenation targets, and if possible by stratifying according to presence or absence of hypoxaemia at baseline. Patient-centred clinical outcomes should also be reported.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Asfar 2017

Methods	RCT 2-by-2 factorial trial randomizing to 4 groups. 2 groups were included in our analysis.
Participants	**Sample size**: 442 randomized (219 experimental, 223 control) **Sex (male)**: experimental 63%, control 65% **Age (mean)**: experimental 67.8, control 66.3 **Country:** France **Setting**: multidisciplinary ICU **Disease severity score:** SAPS III median 71 **Inclusion criteria** 1. Patients aged 18 years and older if they were mechanically ventilated and exhibited septic shock refractory to fluid resuscitation as defined by an absence of response to 20 mL/kg of crystalloids or colloids and requiring vasopressor (norepinephrine or epinephrine, at a minimum infusion rate of 0.1 µg/kg per min); they also had to have been assessed within 6 hours after the initiation of vasopressors. Septic shock was defined by the presence of 2 or more diagnostic criteria of systemic inflammatory response syndrome, proven or suspected infection, and sudden dysfunction of at least 1 organ. **Exclusion criteria** 1. Severe hypoxaemia defined as PaO_2: FiO_2 ratio of less than 100 mmHg for a minimum positive end-expiratory pressure of 5 cm H_2O 2. Plasma sodium concentration of less than 130 mmol/L or more than 145 mmol/L 3. Intracranial hypertension 4. Patient admitted for cardiac arrest 5. Overt cardiac failure

Asfar 2017 *(Continued)*

6. Under legal guardianship
7. No affiliation with the French healthcare system
8. Pregnancy
9. Recent participation in another biomedical study or another interventional study with mortality as the primary endpoint
10. An investigator's decision not to resuscitate

Interventions	**Experimental**: hyperoxia group (mechanical ventilation with FiO_2 of 1.0 for 24 hours after inclusion; thereafter FiO_2 as in the normoxia group). Categorized by us as using a high target in the experimental group. **Control**: target SaO_2 of 88% to 95% using mechanical ventilation **Co-intervention**: not specified **Duration**: 24 hours
Outcomes	**Primary outcome** 1. Death from any cause at day 28 after inclusion **Secondary outcomes** 1. 90-day mortality 2. Daily SOFA from inclusion to day 7 3. 19 days alive and free from organ dysfunction at day 28 4. Length of stay in the ICU 5. Alive at day 28 without organ support was defined as days alive without vasopressor infusion, mechanical ventilation, or renal replacement treatment 6. Safety data (as specified in protocol (NCT01722422) **Outcomes not prespecified** 1. Participants with at least 1 serious adverse event 2. Chest radiograph scores 3. Atelectasis 4. Pneumothorax 5. Ventricular arrhythmias 6. Mesenteric ischaemia 7. Digital ischaemia 8. ICU-acquired weakness 9. Participants with ≥ 1 nosocomial infection during ICU stay 10. Participants with ≥ 1 nosocomial pneumonia during ICU stay
Notes	Email sent to Dr Asfar 5 December 2018 and reply was received. The trial was funded by public grants (the French ministry of health).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list stratified by site and presence or absence of ARDS using permuted blocks of random sizes (nQuery Advisor 6.0)
Allocation concealment (selection bias)	Low risk	The pharmacists assigned a random number to each therapeutic package. The attribution of a given therapeutic package to a participant in accordance to

Asfar 2017 *(Continued)*

		the randomization list was done with a web-based secured randomization system (Clinsight software).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	2.7% in the experimental group and 0.9% in the control were excluded from analysis.
Selective reporting (reporting bias)	Low risk	The trial was registered prior to randomisation (NCT01722422), and all prespecified outcomes were reported on.
Other bias	High risk	Early stopping bias: the trial was stopped after a pre-planned interim analysis, criteria for stopping not specified

Girardis 2016

Methods	RCT
Participants	**Sample size**: 480 (experimental 244, control 236) **Sex (male %)**: experimental 57%, control 56% **Age (median)**: experimental 65, control 63 **Country**: Italy **Setting**: multidisciplinary ICU **Disease severity score**: SAPS II score median 38 **Inclusion criteria** 1. All patients aged 18 years or older and admitted to the ICU with an expected length of stay of 72 hours or longer **Exclusion criteria** 1. Age younger than 18 years 2. Pregnancy 3. ICU readmission 4. A decision to withhold life-sustaining treatment 5. Immunosuppression or neutropenia 6. Enrolment in another study 7. Patients with acute decompensation of COPD and ARDS with a PaO_2:FiO_2 ratio of less than 150
Interventions	**Experimental**: oxygen therapy was administered according to standard ICU practice; FiO_2 of at least 0.4, allowing PaO_2 values up to 150 mmHg and an SpO_2 between 97% and 100%. If the SpO_2 decreased below 95% to 97%, the FiO_2 was increased to reach the target value of SpO_2. Participants received FiO_2 of 1.0 during intubation, airway suction, or hospital transfer.

Girardis 2016 *(Continued)*

	Categorized by us as using a high target in the experimental group. **Control**: oxygen therapy was administered at the lowest possible FiO_2 to maintain the PaO_2 between 70 and 100 mmHg or SpO_2 values between 94% and 98%. FiO_2 was gradually reduced or oxygen supplementation discontinued whenever the PaO_2 or SpO_2 exceeded 100 mmHg or 98%. Supplemental oxygen was administered only if SpO_2 decreased below 94%. Categorized by us as using a high target in the control group. **Co-intervention**: not specified **Duration**: until ICU discharge
Outcomes	1. ICU mortality 2. New-onset respiratory, cardiovascular, liver, and renal failure (defined as a SOFA score ≥ 3 for the corresponding organ) occurring 48 hours or more after ICU admission 3. Need for reoperation in surgical patients 4. Bloodstream, respiratory, and surgical site infections (according to Centers for Disease Control and Prevention definitions). Only microbiologically documented bloodstream and respiratory tract infections were considered. **Secondary outcomes not prespecified** 1. Hospital mortality 2. Ventilation-free hours during the ICU stay
Notes	Email sent 6 December 2018 to Dr Girardis and reply was received. The trial was funded by public grants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	The randomization sequence was concealed from the researchers by use of sequentially numbered, closed, opaque envelopes that were opened after patient study inclusion.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not described; however, blinding of outcome assessment was clarified by email
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results from intention-to-treat analyses are provided in the supplementary. 2 participants withdrew consent, randomization groups for these 2 participants were not reported, thus they could not be included in the sensitivity analysis on losses to follow-up. Outcome respiratory failure: 18 in experimental and 15 in control group were lost to follow-up

Girardis 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	The trial was registered retrospectively (NCT01319643)
Other bias	High risk	Early stopping bias: the trial was stopped after an interim analysis that was not pre-planned

Gomersall 2002

Methods	RCT
Participants	**Sample size**: 36 (experimental 19, control 17) **Sex (male %)**: experimental 82%, control 76% **Age (mean)**: experimental 68, control 69 **Country**: Hong Kong **Setting**: multidisciplinary ICU **Disease severity score:** not reported **Inclusion criteria** 1. Patients admitted with a clinical diagnosis of an acute exacerbation of COPD and a PaO_2 < 6.6 kPa (50 mmHg), and $PaCO_2$ > 6.6 kPa (50 mmHg) on air. **Exclusion criteria** 1. Chest radiologic signs of pulmonary oedema, lung cancer, pneumothorax, or pneumonia 2. If the patient already met study criteria for mechanical ventilation 3. Mechanical ventilation for respiratory failure twice in the preceding 6 months 4. Inability to walk more than 20 yards on flat ground 5. Co-existing terminal disease
Interventions	Oxygen therapy was provided via a Venturi-type mask and adjusted according to the results of arterial blood samples with the aim of reaching the desired target oxygen tension within 1 hour of trial entry. **Experimental**: target PaO_2 above 9.0 kPa (70 mmHg) (categorized by us as using a low target in the experimental group) **Control:** target PaO_2 of > 6.6 kPa (50 mmHg) (categorized by us as using a low target in the control group) **Co-intervention**: participants in the low-oxygen tension group also received doxapram if they developed an acidosis with pH < 7.2, whereas those in the high-oxygen tension group received doxapram if they developed symptomatic acidosis. Bronchodilator, steroid, and antibiotic therapy was standardized. **Duration**: treatment protocols, including oxygen therapy, were continued after discharge from the ICU until oxygen therapy was no longer considered necessary
Outcomes	1. Need for mechanical ventilation 2. Duration of hospital stay 3. Cardiac arrhythmia 4. Mortality 5. Coma

Gomersall 2002 *(Continued)*

Notes	Email sent to Dr Gomersall 6 December 2018 but no reply was received. The trial was funded by public grants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers
Allocation concealment (selection bias)	Low risk	Unmarked, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Only participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	2/19 (11%) of participants in the experimental group were excluded from analysis due to protocol violation.
Selective reporting (reporting bias)	Unclear risk	No protocol could be found.
Other bias	High risk	Doxapram co-intervention differed between groups.

Ishii 2018

Methods	RCT
Participants	**Sample size**: 44 (experimental 21, control 23) **Sex**: not specified **Age**: not specified **Country**: Japen **Setting**: surgical ICU **Disease severity score:** not reported **Inclusion criteria**: mechanically ventilated patients admitted to surgical ICU for more than 12 hours **Exclusion criteria**: not specified
Interventions	**Experimental**: FiO_2 of 1.0 using high-flow nasal cannula. Categorized by us as using a high target in the experimental group **Control**: expected FiO_2 to achieve a PaO_2 of 100 mmHg (13.3 kPa) using high-flow nasal cannula

Ishii 2018 *(Continued)*

	The interventions are 'non-invasive', as they are initiated after extubation (of the mechanical ventilated), whereas after oxygen they are administered via high-flow nasal cannula. Categorized by us as using a low target in the control group **Co-intervention**: not specified **Duration**: 1 hour
Outcomes	1. Atelectasis
Notes	Email sent 6 December 2018 to Dr Ishii but no reply was received. It was unclear how the trial was funded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that the trial was randomized, but method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blinded, but it was unclear who was blinded and how blinding was maintained.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Radiologist was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	14% were lost to follow-up; randomization groups were not reported.
Selective reporting (reporting bias)	Unclear risk	No protocol could be found.
Other bias	Low risk	The trial appeared to be free of other issues that could put it at risk of bias.

Jakkula 2018

Methods	RCT with a 2-by-3 factorial design. We only extracted data from the normoxia and moderate-hyperoxia groups.
Participants	**Sample size**: 123 (experimental 60, control 63) **Sex (male %)**: experimental 48%, control 50% **Age**: experimental 60, control 59 **Country**: Finland **Setting**: adults admitted to the ICU after OHCA **Disease severity score:** APACHE II score median 28

Jakkula 2018 *(Continued)*

Inclusion criteria

1. Adults resuscitated from witnessed OHCA with VF or VT as the initial rhythm. In addition, all of the following inclusion criteria had to be met:
   a. ROSC 10 to 45 minutes from the onset of cardiac arrest;
   b. confirmed or suspected cardiac origin of the arrest;
   c. mechanical ventilation upon ICU arrival;
   d. markedly impaired level of consciousness defined as no response to verbal commands and GCS motor score < 5 (withdrawal to painful stimuli at best);
   e. deferred consent from next of kin possible or likely; and
   f. active intensive care and TTM initiated.

Exclusion criteria

1. Adults with confirmed or suspected acute or pre-existing intracranial pathology or suspicion of increased intracranial pressure, or both
2. Adults with severe oxygenation failure defined as PaO_2/FiO_2 < 100 mmHg upon arrival to ICU and no improvement in oxygenation after adding sufficient PEEP level
3. Severe COPD
4. Age < 18 or > 80 years
5. Pregnancy

Interventions	**Experimental**: target $PaO_2$of 20 to 25 kPa (150 to 187.5 mmHg). Categorized by us as using a high target in the experimental group **Control**: target PaO_2 of 10 to 15 kPa (75 to 112.5 mmHg) or target SpO_2 of 95% to 98%. Categorized by us as using a high target in the control group **Co-intervention**: all adults received TTM at 33 °C or 36 °C and were sedated according to the treating clinicians' instructions. All adults received standard care, monitoring and assessments based on the protocol of the ICU, including direct blood pressure monitoring via an arterial catheter. **Duration**: 36 hours
Outcomes	**Primary outcome** 1. NSE serum concentration at 48 hours after cardiac arrest **Secondary outcomes** 1. NSE serum concentration at 24 and 72 hours after cardiac arrest 2. S100 protein serum concentration at 24, 48, and 72 hours after cardiac arrest 3. TnT concentration at 24, 48, and 72 hours after cardiac arrest 4. Results of NIRS monitoring during the first 48 hours after admission to the ICU 5. Results of continuous EEG monitoring for 48 hours after arrival at the ICU and a statement of the findings by an experienced senior neurologist or neurophysiologist 6. CPC at 6 months after cardiac arrest 7. Total duration of intensive care 8. Total duration of mechanical ventilation 9. Length of hospital stay 10. Discharge destination 11. Vital status at hospital discharge (dead or alive) **Feasibility outcomes** 1. Difference in $PaCO_2$ between groups targeting low to normal (4.5 to 4.7 kPa) and high to normal (5.8 to 6.0 kPa) $PaCO_2$

Jakkula 2018 *(Continued)*

2. Difference in PaO_2 between groups targeting low to normal (10 to 15 kPa) and high to normal (20 to 25 kPa) PaO_2
3. Difference in MAP between groups targeting low to normal (65 to 75 mmHg) and high to normal (80 to 100 mmHg) MAP
4. Distribution of values for primary and secondary outcomes
5. Randomized or screened participant ratio
6. Consent rate
7. Data completion rate
8. Recruitment duration

Notes	Email sent 6 December 2018 to Dr Jakkula but no reply was received. The trial was funded by public and private funds. The funding bodies had no input regarding the design, management, or reporting of the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Web-based system
Blinding of participants and personnel (performance bias) All outcomes	High risk	The treating personnel were not blinded to treatment targets.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The neurophysiologist analysing the EEG results and the neurologist evaluating the neurologic recovery of the participants were blinded to the study group allocations.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% were lost to follow-up.
Selective reporting (reporting bias)	Low risk	The trial was registered prior to randomization (NCT02698917).
Other bias	Low risk	The trial appeared to be free of other issues that could put it at risk of bias.

Lång 2018

Methods	RCT
Participants	**Sample size**: 65 (experimental 38, control 27) **Sex (male)**: experimental 82%, control 85% **Age:** experimental 45, control 43 **Country**: Finland **Setting**: mechanically ventilated adults with traumatic brain disease admitted to the ICU

Lång 2018 *(Continued)*

	Disease severity score: APACHE II score median 22 **Inclusion criteria** 1. Isolated non-penetrating TBI or adults with multiple trauma with TBI with GCS 8 or less (inclusive), expected need for intubation and mechanical ventilation > 24 hours 2. Recruitment within 18 hours after admission to ICU 3. Time from TBI < 36 hours 4. Informed consent from next of kin **Exclusion criteria** 1. Age < 18 or > 65 years 2. Anticipated brain death in 12 hours or otherwise moribund adults expected to die in 24 hours 3. Expected need for mechanical ventilation < 24 hours 4. Insufficient oxygenation assessed by a clinician 5. Adults with multiple trauma with brain injury and severe abdominal, thoracic, or pelvic injury possibly affecting oxygenation 6. No consent 7. Insufficient oxygenation with the treatment modality of the lower oxygenation group (PaO_2 < 13 kPa or SpO_2 < 95% with FiO_2 of 0.40 and PEEP of 10) 8. Oxygenation failure probable during ICU care 9. Penetrating TBI 10. Suspected pregnancy (perform urinary or serological pregnancy test if suspected)
Interventions	**Experimental:** FiO_2 of 0.70. Categorized by us as using a high target in the experimental group **Control**: FiO_2 of 0.40. Categorized by us as using a low target in the control group **Co-intervention**: not specified **Duration**: maximum 14 days
Outcomes	1. Laboratory markers during the first 3 days 2. Pulmonary function (PaO_2/FiO_2 ratio, ARDS, atelectasis, pneumonia) 3. Length of mechanical ventilation 4. Length of ICU stay 5. Length of hospital stay 6. Death 7. Extended Glasgow Outcome Scale
Notes	Email sent 6 December 2018 to Dr Lång and a reply was received. It was unclear how the trial was funded. According to protocol, the trial was supported by Kuopio University Hospital.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that the trial was randomized, but the method of sequence generation was not described
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes

Lång 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only the neurologist assessing the neurological outcomes was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	8% were lost to follow-up, and allocation groups were not specified in the publication. The number of participants lost to follow-up in each group was clarified by email.
Selective reporting (reporting bias)	Low risk	The trial was registered prior to randomization (NCT01201291), however quality of life is not reported; however trial authors are planning to publish these results.
Other bias	High risk	Unplanned trial stop

Mazdeh 2015

Methods	RCT
Participants	**Sample size**: 51 (experimental 26, control 25) **Sex (male %)**: experimental 54%, control 56% **Age**: not specified **Country**: Iran **Setting**: adults with stroke initially referred to the Department of Neurology, but admitted to the ICU **Disease severity score:** not reported **Inclusion criteria** 1. Age between 40 and 70 years 2. GCS > 12 and adults with isolated brain damage and intact airway control 3. Ischaemic and haemorrhagic stroke with no need for surgical intervention 4. Less than 12 hours have passed since the accident 5. NIHSS square between 7 and 9 Quote: "Participants were selected from adults referred to the Department of Neurology of Farshchian Hospital, an affiliated hospital of Hamadan University of Medical Sciences. The participants were admitted to the ICU and monitored by nurses." Due to participants being transferred from the Department of Neurology to the ICU to be monitored, we do not regard these adults as typical adults admitted to the ICU. **Exclusion criteria** 1. Adults under 40 and older than 70 years 2. Adults with diabetes mellitus and ischaemic heart disease, renal failure, acute pulmonary oedema, history of massive myocardial infarction, and heart failure 3. Adults who need intubation on arrival to the hospital 4. Adults with a baseline blood pressure of less than 90/60, or hypoxia 5. Adults requiring surgical intervention (i.e. acute subdural haematoma and cerebral haemorrhage)

Mazdeh 2015 *(Continued)*

	6. Adults with blood pressure greater than 170/90 in the first 12 hours of the incident 7. Adults with successful CPR within 12 hours 8. History of previous stroke or unconsciousness resulting in the need for intubation and mechanical ventilation 9. Death or lost to follow-up 10. Adults in the control group for whom oxygen therapy was inevitable
Interventions	**Experimental**: FiO_2 of 0.5 - oxygen therapy with Venturi mask (categorized by us as using a low target in the experimental group) **Control**: no supplemental oxygen was administered (categorized by us as using a low target in the control group) **Co-intervention**: routine medication (as stated in protocol) **Duration**: oxygen administration was given in the first 12 hours of admission
Outcomes	1. Good recovery and lower number of complications in the first day of admission, before discharge, and 6 months after discharge using ranking scale and Barthel Index (as stated in protocol) 2. Outcome not prespecified: mortality
Notes	Email sent 6 December 2018 to Dr Seifirad, who forwarded the email on to Dr Mazdeh, however no reply was received. The trial was funded by a public hospital (Vice Chancellor of Research and Technology, Hamadan Medical University). Overall poor reporting quality.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that the trial was randomized, but the method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	1 out of 52 (2%) randomized participants was lost to follow-up, and this was not described in the manuscript. It is not stated to which group this person was allocated. Participants in the control group for whom oxygen therapy was inevitable were excluded.
Selective reporting (reporting bias)	High risk	We judged the trial to be registered retrospectively (IRCT201212199647N2). It was registered 3 November 2013 and submitted to journal 30 December 2013.
Other bias	Low risk	The trial appeared to be free of other issues that could put it at risk of bias.

Panwar 2016

Methods	RCT
Participants	**Sample size**: 104 (experimental 51, control 53 (1 lost to follow-up)) **Sex (male %)**: experimental 65%, control 62% **Age**: experimental 62, control 62 **Country**: Australia, New Zealand, and France **Setting**: mechanically ventilated adults admitted to a multidisciplinary ICU **Disease severity score:** APACHE III score median 80 (control) and 70 (experimental) **Inclusion criteria** 1. People admitted to the ICU 2. Aged ≥ 18 years 3. Receiving invasive MV for < 24 hours, and their treating clinician expected MV to continue for at least the next 24 hours The reason for the inclusion criterion of receiving invasive MV for < 24 hours was to ensure that participants who would be assigned to the conservative oxygen group were not exposed to standard liberal oxygen therapy for prolonged periods prior to randomization. **Exclusion criteria** 1. Known pregnancy 2. Imminent risk of death 3. If the treating clinician lacked equipoise for the patient to be enrolled in this trial The exclusion criterion "lacked equipoise" included those clinical situations where the most appropriate approach (conservative versus liberal) to oxygen therapy is well established. For example, in hypercapnic patients with chronic respiratory failure or exacerbation of COPD, there is level I evidence supporting a conservative approach to oxygen therapy (1), and in patients with carbon monoxide poisoning or necrotizing fasciitis a liberal approach is preferred. However, amongst patients who had COPD listed as 1 of the prior comorbid conditions, the treating clinicians could permit enrolment of those adults who were admitted for reasons unrelated to COPD.
Interventions	**Experimental**: SpO_2 target ≥ 96%. Categorized by us as using a high target in the experimental group **Control**: target SpO_2 of 88% to 92%. When FiO_2 requirement was < 0.50, an SpO_2 of 90% to 92% was recommended, and when FiO_2 requirement was ≥ 0.50, an SpO_2 of 88% to 90% was recommended. Categorized by us as using a low target in the control group **Co-intervention**: participating sites were requested to adhere to best practice guidelines in relation to other potentially confounding co-interventions such as adjustment of tidal volume, PEEP, fluid management, blood transfusion, muscle relaxation, sedation interruption, ventilator weaning, nutrition, use of steroids, early mobilization, and physiotherapy. **Duration**: entire duration of mechanical ventilation
Outcomes	**Primary outcomes** 1. Proportion of time spent in the assigned SpO_2 range in each arm 2. Area under the curve for PaO_2, FiO_2, and SpO_2 on day 0 to day 7 in each arm **Secondary outcomes** 1. Incidence of circulation-related events

Panwar 2016 *(Continued)*

2. Incidence of respiration-related events
3. Incidence of acute kidney injury
4. Incidence of outcomes related to other organ systems
5. Time to successful extubation (alive and extubated for > 48 hours)
6. MV-free days
7. ICU mortality
8. Hospital mortality
9. All-cause mortality

Notes	Email sent to Dr Panwar 5 December 2018. Reminder sent 10 December 2018; reply was received. The trial was supported by public grants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were unaware of their assigned group, but blinding of treating clinicians was not considered feasible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described; however, Dr Panwar clarified in an email that outcome assessment was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 (1/104) participant was lost to follow-up.
Selective reporting (reporting bias)	Low risk	A study protocol was registered prior to randomization (ACTRN12613000505707), and all outcomes were reported on.
Other bias	Low risk	The trial appeared to be free of other issues that could put it at risk of bias.

Taher 2016

Methods	RCT
Participants	**Sample size**: 68 (experimental 34, control 34) **Sex (male %)**: experimental 74%, control 68% **Age**: experimental 40, control 46 **Country**: Iran **Setting**: adults with traumatic brain injury initially referred to the emergency department, but who were admitted to the ICU **Disease severity score:** GCS score mean 7.4

Taher 2016 *(Continued)*

	Inclusion criteria 1. Age between 18 and 65 years 2. Less than 6 hours passed since the accident; haemodynamic stability; and GCS between 3 and 8 **Exclusion criteria** 1. Pregnancy 2. People under 18 or older than 65 years 3. GCS under 3 or more than 8 4. People with chronic disease such as diabetes mellitus, ischaemic heart disease, renal failure, acute pulmonary oedema, history of massive myocardial infarction, and heart failure 5. People with a baseline blood pressure of less than 90/60 6. People with successful CPR 7. Death or loss to follow-up Participants in the control group for whom oxygen therapy was inevitable were also excluded from this study.
Interventions	**Experimental**: FiO_2 of 80% oxygen by mechanical ventilator in the first 6 hours after the traumatic accident. Categorized by us as using a high target in the experimental group **Control**: FiO_2 of 0.5 using mechanical ventilator in the first 6 hours after the traumatic accident. Categorized by us as using a low target in the control group **Co-intervention**: not specified **Duration**: 6 hours
Outcomes	1. Glasgow Coma Scale 2. Barthel Index 3. mRS neurologic disability scoring system at the time of discharge from hospital and at 6-month follow-up
Notes	No relevant outcomes reported. Participants who died were excluded (from analyses). Email sent 6 December 2018 to Dr Pilehvari but no reply was received. The trial was funded by public funds.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that the trial was randomized, but sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blind; however, it was unclear who was blinded and how blinding was maintained.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described

Taher 2016 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants who died or were lost to follow-up were excluded.
Selective reporting (reporting bias)	Unclear risk	No protocol could be found.
Other bias	Low risk	The trial appeared to be free of other issues that could put it at risk of bias.

Young 2017

Methods	RCT
Participants	**Sample size**: 100 (experimental 51, control 49 (48 analysed)) **Sex (male %)**: experimental 67%, control 65% **Age**: experimental 60, control 61 **Country**: New Zealand **Setting**: mechanically ventilated adults admitted to a multidisciplinary ICU **Disease severity score:** APACHE II score median 22.1 **Inclusion criteria** 1. People at least 18 years of age who require invasive mechanical ventilation in the ICU and are expected to be receiving mechanical ventilation beyond the next calendar day **Exclusion criteria** 1. Greater than 2 hours of invasive mechanical ventilation or non-invasive ventilation, or both, in an ICU during this hospital admission (includes time ventilated in another hospital's ICU) 2. In the view of the treating clinician, hyperoxia is clinically indicated for reasons including (but not limited to) carbon monoxide poisoning or a requirement for hyperbaric oxygen therapy 3. In the view of the treating clinician, avoidance of hyperoxia is clinically indicated for reasons including (but not limited to) COPD, paraquat poisoning, previous exposure to bleomycin, or chronic hypercapnic respiratory failure 4. Pregnancy 5. Death is deemed to be inevitable as a result of the current acute illness, and either the treating clinician, the participant, or the substitute decision-maker is not committed to full active treatment 6. Adults with a life expectancy of less than 90 days due to a chronic or underlying medical condition 7. Admitted following a drug overdose (including alcohol intoxication) 8. Long-term dependence on invasive ventilation prior to this acute illness 9. Confirmed or suspected diagnosis of any of the following: Guillain-Barré syndrome, cervical cord injury above C5, muscular dystrophy, or motor neuron disease 10. Enrolment not considered to be in the patient's best interest 11. Enrolled in any other trial of targeted oxygen therapy 12. Previously enrolled in the ICU-ROX study
Interventions	**Experimental**: no specific measures taken to avoid high FiO_2 or SpO_2, FiO_2< 0.30 discouraged (thus we could not categorize the experimental group as using either a low or high target). Participants assigned to the 'higher group' received 'standard care' both whilst ventilated and after extubation with no specific measures taken to avoid high FiO_2 or high SpO_2. The use of upper alarm limits for SpO_2 in

Young 2017 *(Continued)*

	the higher group was prohibited, as upper alarm limits for SpO_2 were not used as part of standard care. The lower limit alarm for SpO_2 was set at 90% (or lower if clinically appropriate). If the PaO_2 or SaO_2 was lower than the acceptable limit, inspired oxygen might be increased if clinically appropriate, irrespective of the SpO_2 reading. The use of an FiO_2 of less than 0.3 whilst ventilated was discouraged. **Control**: target SaO_2/SpO_2 91% to 96%. When a participant was allocated to conservative oxygen therapy, the inspired oxygen concentration was decreased to room air as rapidly as possible provided that the SpO_2 measured by peripheral pulse oximetry was greater than the acceptable lower limit. SpO_2 levels of greater than 96% were strictly avoided, and an upper SpO_2 alarm limit of 97% applied whenever supplemental oxygen was administered in the ICU to minimize the risk of hyperoxaemia. After extubation, in the conservative oxygen group, the upper monitored alarm limit of acceptable SpO_2 of 97% was applied whenever supplemental oxygen was being administered. In the event that the SpO_2 exceeded the acceptable upper limit, downward titration of supplemental oxygen was undertaken as a high priority and supplemental oxygen was discontinued as soon possible. The lower limit alarm for SpO_2 was set at 90% (or lower if clinically appropriate). If the PaO_2 or SaO_2 was lower than the acceptable limit, inspired oxygen might be increased if clinically appropriate, irrespective of the SpO_2 reading. Categorized by us as using a low target in the control group **Co-intervention**: there were no restrictions on concomitant treatments provided to participants. If an increase in FiO_2 for procedures performed in the ICU included (but were not limited to) bronchoscopy, suctioning, tracheostomy, or preparation for extubation, this was permitted in both groups. **Duration**: until death or discharge from the ICU, or day 28 postrandomization
Outcomes	*Outcomes that will be reported in the final trial report: 1. Ventilator-free days 2. All-cause mortality (day 90 and day 180) 3. Duration of survival 4. Quality of life 5. Functional outcome assessed by the extended Glasgow Outcome Scale 6. Proportion of participants in paid employment at baseline who are unemployed at 180 days 7. Cognitive function
Notes	*The trial report included data from a pilot phase of the ICU-ROX trial. It included the first 100 patients of an overall sample of 1000, which was to examine the feasibility. Only feasibility outcomes were reported, and outcomes prespecified in protocol will be reported in final trial report including 1000 participants, thus no relevant outcomes were reported. Email sent 6 December 2018 to Dr Young and reply was received. The trial was supported by public funds.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Encrypted web-based system
Allocation concealment (selection bias)	Low risk	Central randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded

Young 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not described; however, blinding of outcome assessment was clarified by email
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 5% were lost to follow-up.
Selective reporting (reporting bias)	Low risk	The trial was registered prior to randomization (ACTRN12615000957594). Only feasibility outcomes were reported, and outcomes prespecified in the protocol will be reported in the final trial report including 1000 participants. However, mortality is reported in total (30.3%), but is not specified according to treatment group.
Other bias	Low risk	The trial appeared to be free of other issues that could put it at risk of bias.

APACHE II**:** Acute Physiology, Age, Chronic Health Evaluation II**; ARDS**: acute respiratory distress syndrome; **AUC**: area under the curve; **C5**: cervical spine vertebral level 5; **COPD**: chronic obstructive pulmonary disease; **CPC**: cerebral performance category; **CPR**: cardiopulmonary resuscitation; **EEG**: electroencephalogram; **FiO_2:** fraction of inspired oxygen; **GCS**: Glasgow Coma Scale; **H_2O**: dihydrogen monoxide (water); **ICU**: intensive care unit; **MAP**: mean arterial pressure; **mRS**: modified ranking scale; **MV**: mechanical ventilation; **NIRS**: cerebral near-infrared spectroscopy; **NIHSS**: National Institutes of Health Stroke Scale; **NSE**: neuron-specific enolase; **OHCA**: out-of-hospital cardiac arrest; **$PaCO_2$**: partial pressure of arterial carbon dioxide; **PaO_2**: partial pressure of arterial oxygen; **PEEP**: positive end-expiratory pressure; **PaO_2/FiO_2 ratio**: ratio of arterial oxygen partial pressure to fractional inspired oxygen; **RCT**: randomized controlled trial; **ROSC**: return of spontaneous circulation; **SaO_2:** arterial oxygen saturation of haemoglobin; **SAPS**: simplified acute physiology score; **SOFA**: sequential organ failure assessment; **SpO_2**: peripheral oxygen saturation; **TBI**: traumatic brain injury; **TnT**: cardiac troponin; **TTM**: targeted temperature management; **VF**: ventricular fibrillation; **VT**: ventricular tachycardia

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ali 2013	Wrong population
Amar 1994	Wrong population
Austin 2010	Wrong population
Bickel 2011	Wrong population
Bray 2018	Wrong population
Hofmann 2017	Wrong population
Huynh Ky 2017	Wrong population
Khoshnood 2018	Wrong population
Khosnood 2017	Wrong population
Kuisma 2006	Wrong population
Meyhoff 2009	Wrong population
Padma 2010	Wrong population

Study	Reason for exclusion
Perrin 2011	Wrong population
Ranchord 2012	Wrong population
Rawles 1976	Wrong population
Rodrigo 2003	Wrong population
Roffe 2010	Wrong population
Roffe 2017	Wrong population
Sills 2003	Wrong population
Singhal 2005	Wrong population
Singhal 2013	Wrong population
Stub 2014	Wrong population
Ukholkina 2005	Wrong population
Wu 2014	Wrong population
Young 2014	Wrong population
Zughaft 2013	Wrong population

Characteristics of studies awaiting assessment *[ordered by study ID]*

ICU-ROX 2019

Methods	RCT
Participants	**Sample size**: 1000 (experimental 501, control 499) **Country**: New Zealand **Setting**: mechanically ventilated adults admitted to a multidisciplinary ICU
Interventions	**Experimental**: no specific measures taken to avoid high FiO_2 or SpO_2, FiO_2<0.30 discouraged (thus, we could not categorize the experimental group as either using a low or a high target). Patients assigned to the 'higher group' received 'standard care' both while ventilated and after extubation with no specific measures taken to avoid high FiO_2 or high SpO_2. The use of upper alarm limits for SpO_2 in the 'higher group' was prohibited as upper alarm limits for SpO_2 were not used as part of standard care. The lower limit alarm for SpO_2 was set at 90% (or lower if clinically appropriate). If the PaO_2 or the SaO_2 were lower than the acceptable limit, inspired oxygen might be increased if clinically appropriate, irrespective of the SpO_2 reading. The use of an FiO_2 of less than 0.3 whilst ventilated was discouraged. **Control**: target SaO_2/SpO_2 91% to 96%. When a participant was allocated to conservative oxygen therapy, the inspired oxygen concentration was decreased to room air as rapidly as possible provided that the SpO_2 measured by peripheral pulse oximetry was greater than the acceptable lower limit. SpO_2 levels of greater than 96% were strictly avoided and an upper SpO_2 alarm limit of 97%

ICU-ROX 2019 *(Continued)*

	applied whenever supplemental oxygen was administered in the ICU to minimise the risk of hyperoxaemia. After extubation, in the conservative oxygen group, the upper monitored alarm limit of acceptable SpO_2 of 97% was applied whenever supplemental oxygen was being administered. In the event that the SpO_2 exceeded the acceptable upper limit, downward titration of supplemental oxygen was undertaken as a high priority and supplemental oxygen was discontinued as soon possible. The lower limit alarm for SpO_2 was set at 90% (or lower if clinically appropriate). If the PaO_2 or the SaO_2 were lower than the acceptable limit, inspired oxygen might be increased if clinically appropriate, irrespective of the SpO_2 reading. Categorized by us as using a low target in the control group. **Duration**: until death or discharge from the ICU, or day 28 post randomization
Outcomes	**Primary outcome:** 1. Ventilator free days to day 28 **Secondary outcomes:** 1. All-cause mortality (day 90 and 180) 2. Duration of survival 3. Proportion of participants in paid employment at baseline who were unemployed at 180 days 4. Cognitive function at day 180 5. Quality of life at day 180 6. Cause-specific mortality Functional outcome assessed by the extended Glasgow outcome scale (in patients with acute brain pathologi)
Notes	The ICU-ROX trial was published post our literature search and thus was not included in this review. The ICU-ROX trial will be included in a review update.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02321072

Trial name or title	The effects of hyperoxia on organ dysfunction and outcome in critically ill patients with SIRS (O_2-ICU)
Methods	RCT
Participants	Patients admitted to the ICU with ≥ 2 positive SIRS criteria and an expected ICU stay of more than 48 hours
Interventions	**Active comparator: high-normal PaO_2** In participants requiring respiratory monitoring, supplemental oxygen is titrated to achieve a PaO_2 of 120 mmHg (16 kPa), range 105 to 135 mmHg (14 to 18 kPa). **Active comparator: low-normal PaO_2** In participants requiring respiratory monitoring, supplemental oxygen is titrated to achieve a target PaO_2 of 75 mmHg (10 kPa), range 60 to 90 mmHg (8 to 18 kPa).
Outcomes	**Primary outcome** 1. Daily delta SOFA score (time frame: 14 days)

NCT02321072 *(Continued)*

	Secondary outcomes: 1. Total maximum SOFA score minus SOFA score on admission (time frame: 14 days) 2. SOFA rate of decline (time frame: 14 days) 3. Total maximum SOFA score, total maximum SOFA score minus SOFA score on admission, SOFA rate of decline (time frame: 14 days) 4. Mortality (time frame: 14 days, in-ICU (max 90 days), in-hospital (max 90 days) 5. Hypoxic events (PaO_2 < 55 mmHg) (time frame: 14 days) 6. Vasopressor or inotrope requirements (time frame: 14 days) 7. Renal function, fluid balance (time frame: 14 days) 8. Oxidative stress (F2-isoprostanes) (time frame: days 1, 3, 7) 9. Duration of mechanical ventilation and ventilator-free days (time frame: 14 days) 10. Length of stay (ICU) (time frame: average expected 2 to 28 days) 11. Length of stay (hospital) (time frame: average expected 10 to 28 days) 12. Systemic vascular resistance index (time frame: 14 days) in a random subpopulation 13. Cardiac index (time frame: 14 days) in a random subpopulation 14. Microcirculatory flow index and perfused vessel density (time frame: 14 days) in a random sub-population. Composite endpoint for 2 sidestream dark-field microcirculatory measurements
Starting date	February 2015
Contact information	Dr HJS de Grooth
Notes	

NCT02713451

Trial name or title	Liberal oxygenation versus conservative oxygenation in ARDS ($LOCO_2$)
Methods	RCT
Participants	Patients with ARDS
Interventions	**Active comparator: liberal oxygenation (LO) group** A modulation of inspired fraction of oxygen will be performed with an objective of PaO_2 between 90 to 105 mmHg, which will be checked on ABG. Between these measurements, SpO_2 will be kept at ≥ 96%. Alarms will be set at 95% for SpO_2. **Experimental: conservative oxygenation (CO) group** A modulation of inspired fraction of oxygen will be performed with an objective of PaO_2 between 55 to 70 mmHg, which will be checked on ABG. Between these measurements, SpO_2 will be kept between 88% and 92%. Alarms will be set between 87% and 93% for SpO_2.
Outcomes	**Primary outcome** 1. Death (time frame: day 28) **Secondary outcomes** 1. Death (time frame: day 90) 2. Days free of mechanical ventilation in ICU (time frame: day 28) 3. SOFA score (time frame: days 0, 3, and 7)

NCT02713451 *(Continued)*

	4. Score of morbidity (time frame: day 28). This score is based on 3 points: need for mechanical ventilation, need for renal replacement therapy, need for catecholamine. 5. Ventilator-associated pneumonia (time frame: day 28) 6. Septicaemia (time frame: day 28) 7. Antibiotic consumption (time frame: day 28) 8. Cardiovascular complications (time frame: day 28 and day 90). New onset of rhythm disorders, cardiac ischaemia, and dose of catecholamine at days 28 and 90 9. Neurological evolution (time frame: day 28). Neurological evolution measured with daily Richmond Agitation Sedation Scale score, seizures, new stroke, daily sedation doses, neuroleptic administration. 10. Respiratory autonomy (time frame: days 28 and 90). Need for oxygen or mechanical ventilation support
Starting date	June 2016
Contact information	Loïc Barrot
Notes	

NCT03141099

Trial name or title	Blood pressure and oxygenation targets in post-resuscitation care (BOX)
Methods	RCT
Participants	Comatose OHCA patients
Interventions	**Active comparator: low normal MAP and low normal PaO_2** MAP 63 mmHg and PaO_2 9 to 10 kPa during targeted temperature management (36 hours) after OHCA **Active comparator: high normal MAP and low normal PaO_2** MAP 77 mmHg and PaO_2 9 to 10 kPa during targeted temperature management (36 hours) after OHCA **Active comparator: low normal MAP and high normal PaO_2** MAP 63 mmHg and PaO_2 13 to 14 kPa during targeted temperature management (36 hours) after OHCA **Active comparator: high normal MAP and high normal PaO_2** MAP 77 mmHg and PaO_2 13 to 14 kPa during targeted temperature management (36 hours) after OHCA
Outcomes	**Primary outcome** 1. All-cause mortality or severe anoxic brain injury (time frame: 3 months after OHCA) **Secondary outcomes** 1. Renal replacement therapy (time frame: 3 months) 2. Time to death (time frame: 180 days) 3. Neuron-specific enolase (time frame: 48 hours) 4. MOCA score (time frame: 3 months)

NCT03141099 *(Continued)*

5. Modified Ranking Scale (time frame: 3 months)
6. NT-pro-BNP (time frame: 3 months)
7. eGFR (time frame: 3 months)
8. LVEF (time frame: 3 months)
9. Vasopressor use (time frame: first week after cardiac arrest)
10. Renal function (time frame: 96 hours)

Other outcome measures

1. Vital status at 180 days post-cardiac arrest (time frame: 180 days post-cardiac arrest)
2. CPC at 180 days post-cardiac arrest (time frame: 180 days post-cardiac arrest)

Starting date	March 2017
Contact information	Dr Jesper Kjaergaard
Notes	

NCT03174002

Trial name or title	Handling oxygenation targets in adults with acute hypoxaemic respiratory failure in the intensive care unit (HOT-ICU)
Methods	RCT
Participants	ICU patients
Interventions	**Experimental: low oxygenation target** Partial pressure of oxygen in arterial blood (PaO_2) 8 kPa (60 mmHg) **Active comparator: high oxygenation target** Partial pressure of oxygen in arterial blood (PaO_2) 12 kPa (90 mmHg)
Outcomes	**Primary outcome** 1. 90-day mortality (time frame: 90 days) **Secondary outcomes** 1. Days alive without organ support (time frame: within 90 days) 2. Days alive out of the hospital (time frame: within 90 days) 3. Number of participants with 1 or more serious adverse events (time frame: until ICU discharge, maximum 90 days) 4. 1-year mortality (time frame: 1 year) 5. Quality of life assessment using the EQ-5D-5L telephone interview in selected sites (time frame: 1 year) 6. Cognitive function 1-year after randomization as assessed using the RBANS score in selected sites (time frame: 1 year) 7. Pulmonary function (time frame: 1 year) 8. A health economic analysis (time frame: 90 days)
Starting date	June 2017

NCT03174002 *(Continued)*

Contact information	Dr Bodil Steen Rasmussen
Notes	

NCT03287466

Trial name or title	A randomised controlled trial of targeted oxygen therapy in mechanically ventilated critically ill patients (TOXYC)
Methods	RCT
Participants	Mechanically ventilated adults
Interventions	**Experimental: SpO_2 88% to 92%** The intervention is TO2T to achieve an arterial haemoglobin oxygen saturation (SpO_2) of 88% to 92%. **Active comparator: SpO_2 96% or above** The control group will also receive TO2T, but to achieve an SpO_2 of 96% or above (standard care).
Outcomes	**Primary outcome measures** 1. Feasibility (time frame: 15 months) **Secondary outcomes** 1. Measurement of ABG (time frame: up to 21 days) 2. Measurement of oxygen saturation (time frame: up to 21 days) 3. Measurement of fraction of inspired oxygen (time frame: up to 21 days) 4. Time to extubation or detachment from mechanical ventilation (time frame: up to 21 days) 5. Mechanical ventilation-free days on ICU (time frame: up to 21 days) 6. Measurement of blood pressure (time frame: up to 21 days) 7. Measurement of heart rate (time frame: up to 21 days) 8. Measurement of cardiac rhythm (time frame: up to 21 days) 9. Measurement of cardiac output and stroke volume (if measured) (time frame: up to 21 days) 10. Measurement of vasopressor doses (time frame: up to 21 days) 11. Measurement of inotrope doses (time frame: up to 21 days) 12. Measurement of daily fluid balance (time frame: up to 21 days) 13. Measurement of inotrope-free days on ICU (time frame: up to 21 days) 14. Measurement of vasopressor-free days on ICU (time frame: up to 21 days) 15. Measurement of urea (time frame: up to 21 days) 16. Measurement of creatinine (time frame: up to 21 days) 17. Measurement of urine output (time frame: up to 21 days) 18. Need for renal replacement therapy (time frame: up to 21 days) 19. Renal replacement therapy-free days on ICU (time frame: up to 21 days) 20. Measurement of transaminases (time frame: up to 21 days) 21. Measurement of blood clotting values (time frame: up to 21 days) 22. Measurement of bilirubin (time frame: up to 21 days) 23. Measurement of blood lactate (time frame: up to 21 days) 24. Measurement of troponin (time frame: up to 21 days) 25. Adverse events (time frame: 90 days)

NCT03287466 *(Continued)*	26.SOFA score change (time frame: up to 21 days) 27.APACHE II score change (time frame: up to 21 days) 28.Length of ICU stay (time frame: up to 21 days) 29.Length of hospital stay (time frame: 90 days) 30.Mortality rates (time frame: 90 days) 31.Days alive out of hospital (time frame: 90 days)
Starting date	January 2018
Contact information	Dr Jack D Grierson
Notes	

ABG: arterial blood gases; **APACHE**: Acute Physiology, Age, Chronic Health Evaluation; **ARDS**: acute respiratory distress syndrome; **CO**: conservative oxygenation; **CPC**: cerebral performance category; **eGFR**: estimated glomerular filtration rate; **EQ-5D-5L:** an instrument for measuring quality of life; **FiO_2**: fraction of inspired oxygen; **ICU**: intensive care unit; **LVEF**: left ventricular ejection fraction; **LO**: liberal oxygenation; **MAP**: mean arterial pressure; **MOCA**: Montreal Cognitive Assessment; **NT-pro-BNP**: cardiac biomarker; **OHCA**: out-of-hospital cardiac arrest; **PaO_2**: partial pressure of arterial oxygen; **RBANS**: Repeatable Battery for the Assessment of Neuropsychological Status; **RCT**: randomized controlled trial; **SaO_2**: arterial oxygen saturation of haemoglobin; **SIRS**: systemic inflammatory response syndrome; **SOFA**: sequential organ failure assessment; **SpO_2**: peripheral oxygen saturation; **TO2T**: targeted oxygen therapy

DATA AND ANALYSES

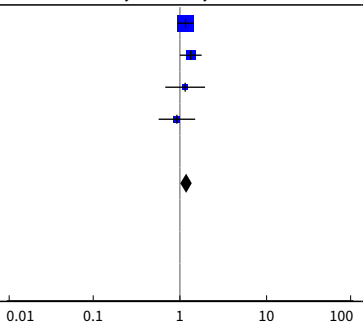
Comparison 1. All-cause mortality - at time point closest to 3 months follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality - at time point closest to 3 months	4	1135	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.01, 1.37]
2 Sensitivity analysis: all-cause mortality - at time point closest to 3 months - high vs high and low vs low targets excluded	2	537	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.92, 1.35]
3 Sensitivity analysis: all-cause mortality - at time point closest to 3 months - best-worst-case scenario	4	1149	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.97, 1.31]
3.1 All-cause mortality	4	1149	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.97, 1.31]
4 Sensitivity analysis: all-cause mortality - at time point closest to 3 months - worst-best-case scenario	4	1149	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.04, 1.41]
4.1 All-cause mortality	4	1149	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.04, 1.41]
5 All-cause mortality - at time point closest to 3 months - types of oxygen interventions	4	1135	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.01, 1.37]
5.1 PaO_2 (SaO_2 or SpO_2)	3	701	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.96, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Difference between groups	1	434	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.94, 1.43]
6 All-cause mortality - at time point closest to 3 months - level of FiO_2/target in higher group	4	1135	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.01, 1.37]
6.1 Higher	4	1135	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.01, 1.37]
7 All-cause mortality - at time point closest to 3 months - level of FiO_2/target in lower group	4	1135	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.01, 1.37]
7.1 Lower	2	537	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.92, 1.35]
7.2 Higher	2	598	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.00, 1.66]
8 All-cause mortality - at time point closest to 3 months - ICU population	4	1135	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.02, 1.38]
8.1 Mixed ICU	3	1015	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.01, 1.40]
8.2 Any cerebral disease	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.68, 1.95]
9 Mortality - at time point closest to 3 months - oxygen delivery system	4	1135	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.02, 1.38]
9.1 Invasive mechanical ventilation	3	657	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.93, 1.34]
9.2 Mixed	1	478	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.00, 1.78]

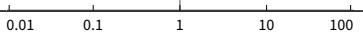
Analysis 1.1. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 1 All-cause mortality - at time point closest to 3 months.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Asfar 2017	104/217	90/217		53.04%	1.16[0.94,1.43]
Girardis 2016	80/243	58/235		28.57%	1.33[1,1.78]
Jakkula 2018	20/59	18/61		8.45%	1.15[0.68,1.95]
Panwar 2016	19/51	21/52		9.94%	0.92[0.57,1.5]
Total (95% CI)	**570**	**565**		**100%**	**1.18[1.01,1.37]**
Total events: 223 (Higher), 187 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=1.75, df=3(P=0.63); I^2=0%					
Test for overall effect: Z=2.08(P=0.04)					



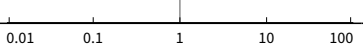
Analysis 1.2. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 2 Sensitivity analysis: all-cause mortality - at time point closest to 3 months - high vs high and low vs low targets excluded.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asfar 2017	104/217	90/217		81.23%	1.16[0.94,1.43]
Panwar 2016	19/51	21/52		18.77%	0.92[0.57,1.5]
Total (95% CI)	**268**	**269**		**100%**	**1.11[0.92,1.35]**
Total events: 123 (Higher), 111 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=0.7, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=1.08(P=0.28)					



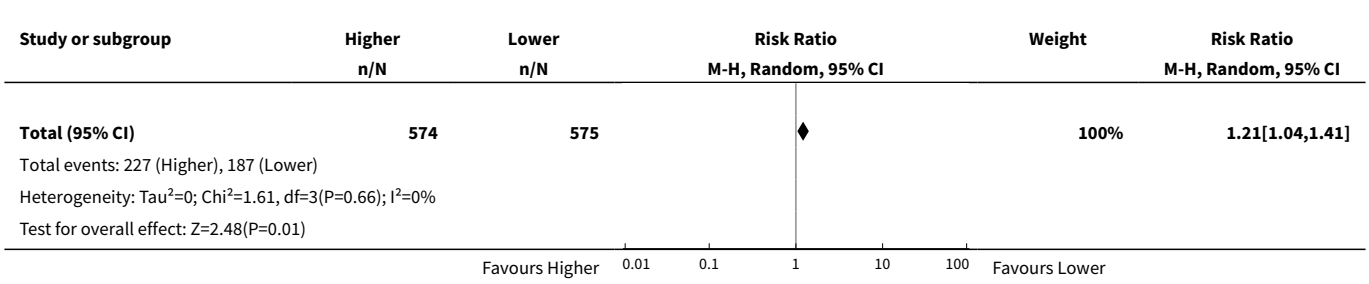
Analysis 1.3. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 3 Sensitivity analysis: all-cause mortality - at time point closest to 3 months - best-worst-case scenario.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 All-cause mortality					
Asfar 2017	104/219	96/223		53.56%	1.1[0.9,1.35]
Girardis 2016	80/244	59/236		27.86%	1.31[0.99,1.74]
Jakkula 2018	20/60	20/63		8.72%	1.05[0.63,1.75]
Panwar 2016	19/51	22/53		9.87%	0.9[0.56,1.45]
Subtotal (95% CI)	**574**	**575**		**100%**	**1.13[0.97,1.31]**
Total events: 223 (Higher), 197 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=2.09, df=3(P=0.55); I^2=0%					
Test for overall effect: Z=1.59(P=0.11)					
Total (95% CI)	**574**	**575**		**100%**	**1.13[0.97,1.31]**
Total events: 223 (Higher), 197 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=2.09, df=3(P=0.55); I^2=0%					
Test for overall effect: Z=1.59(P=0.11)					

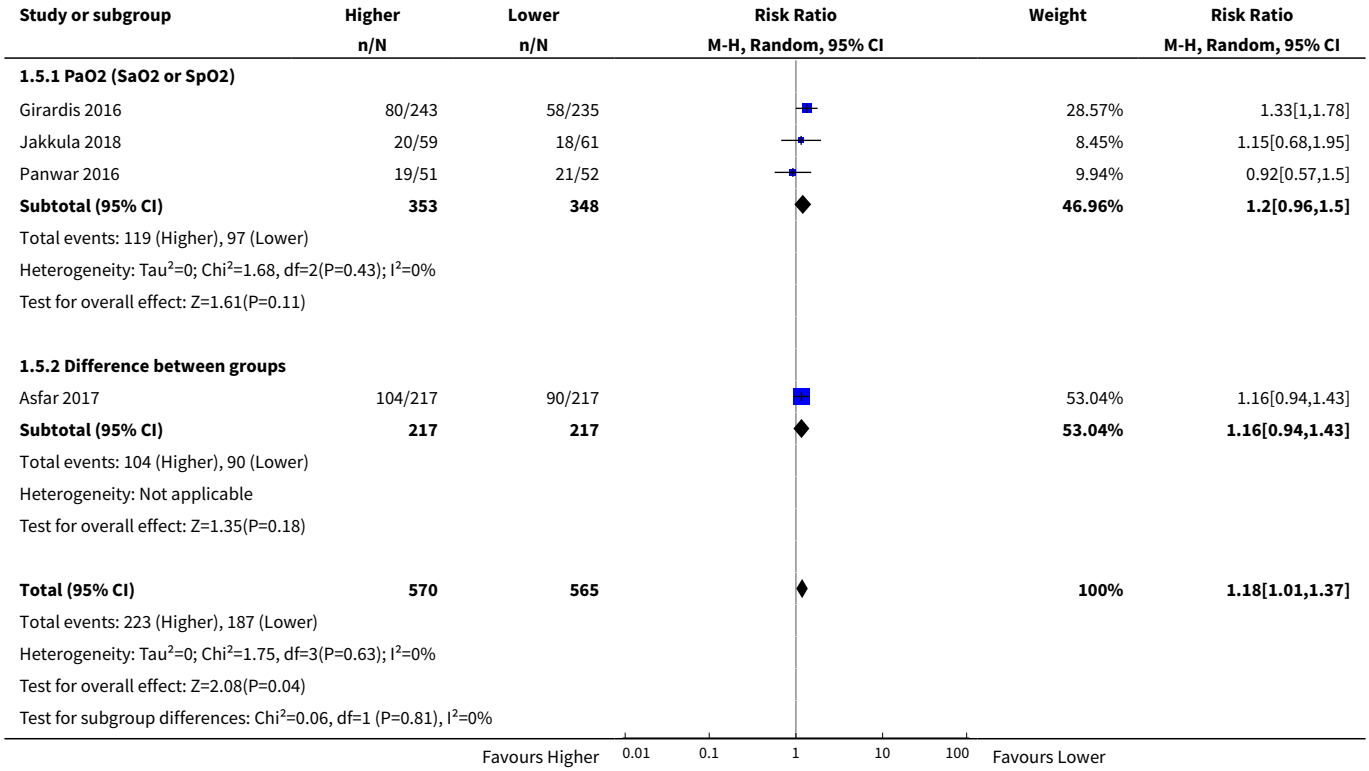


Analysis 1.4. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 4 Sensitivity analysis: all-cause mortality - at time point closest to 3 months - worst-best-case scenario.

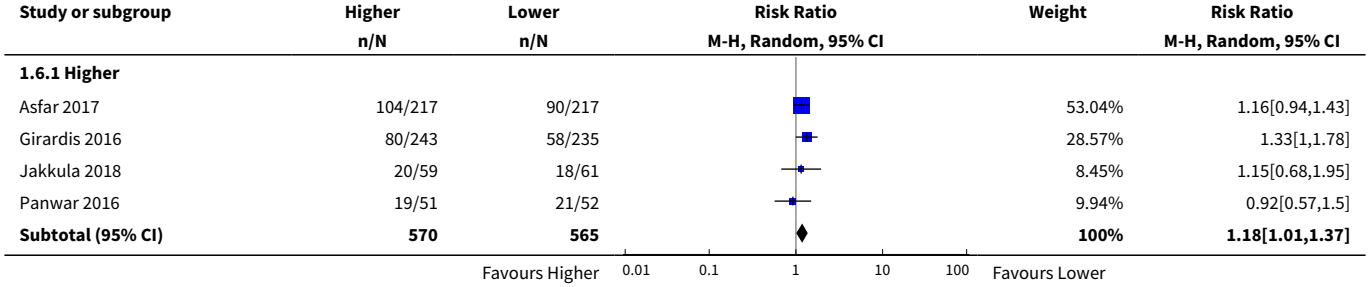
Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 All-cause mortality					
Asfar 2017	106/219	90/223		52.92%	1.2[0.97,1.48]
Girardis 2016	81/244	58/236		28.62%	1.35[1.02,1.8]
Jakkula 2018	21/60	18/63		8.61%	1.23[0.73,2.06]
Panwar 2016	19/51	21/53		9.85%	0.94[0.58,1.53]
Subtotal (95% CI)	**574**	**575**		**100%**	**1.21[1.04,1.41]**
Total events: 227 (Higher), 187 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=1.61, df=3(P=0.66); I^2=0%					
Test for overall effect: Z=2.48(P=0.01)					

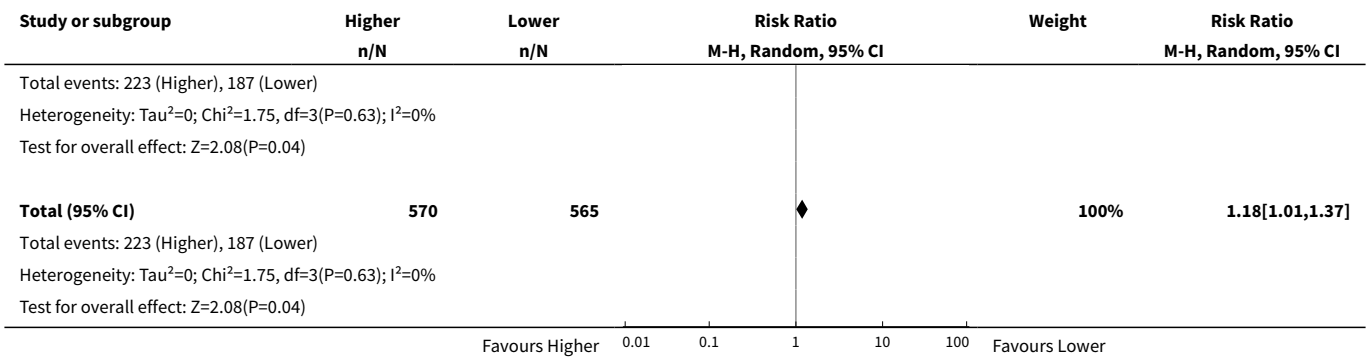


Analysis 1.5. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 5 All-cause mortality - at time point closest to 3 months - types of oxygen interventions.

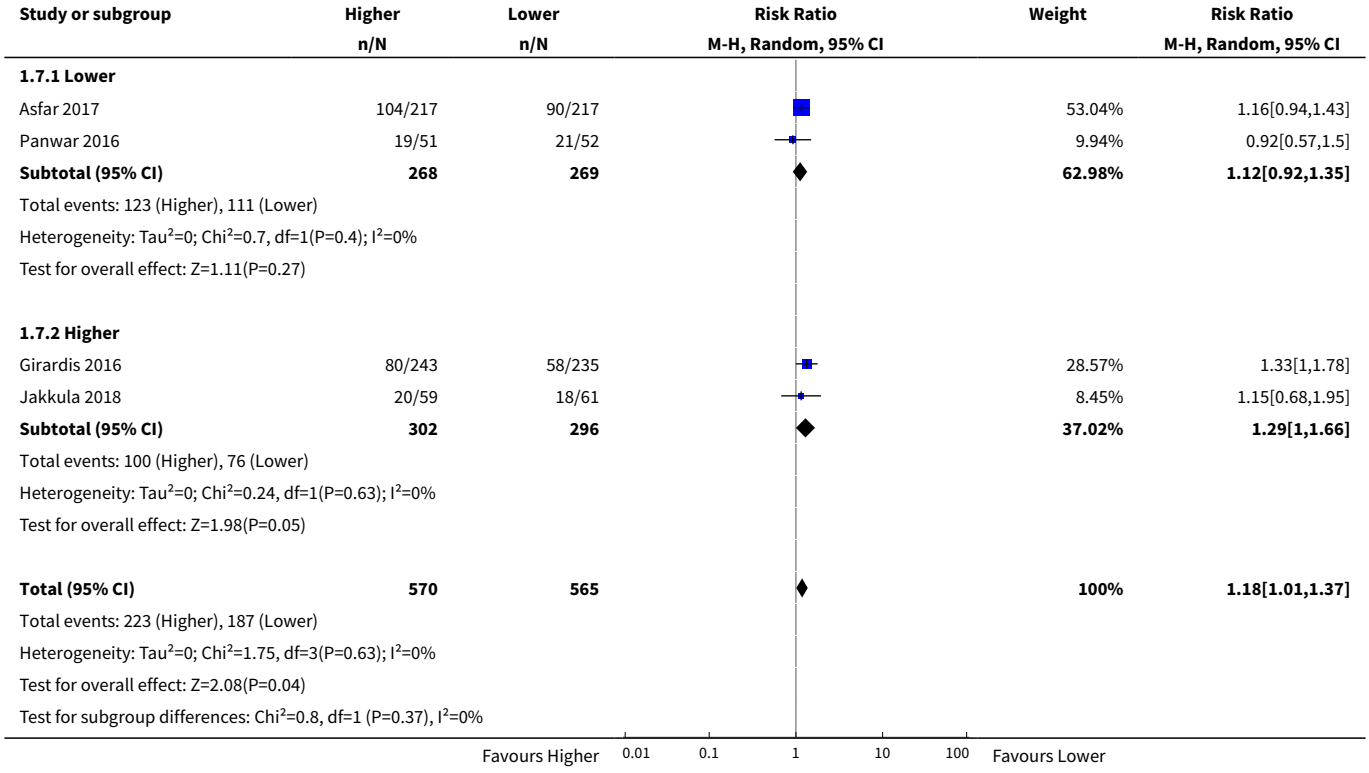


Analysis 1.6. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 6 All-cause mortality - at time point closest to 3 months - level of FiO_2/target in higher group.

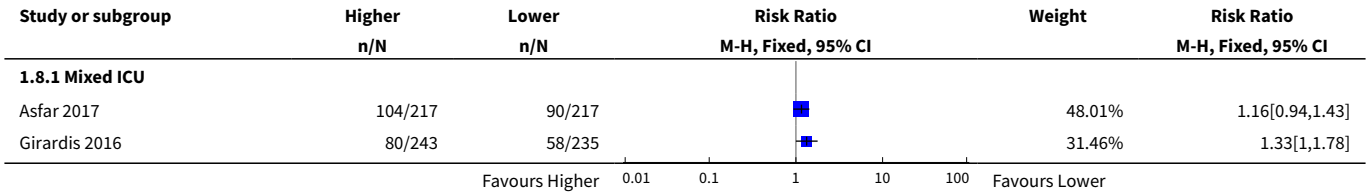


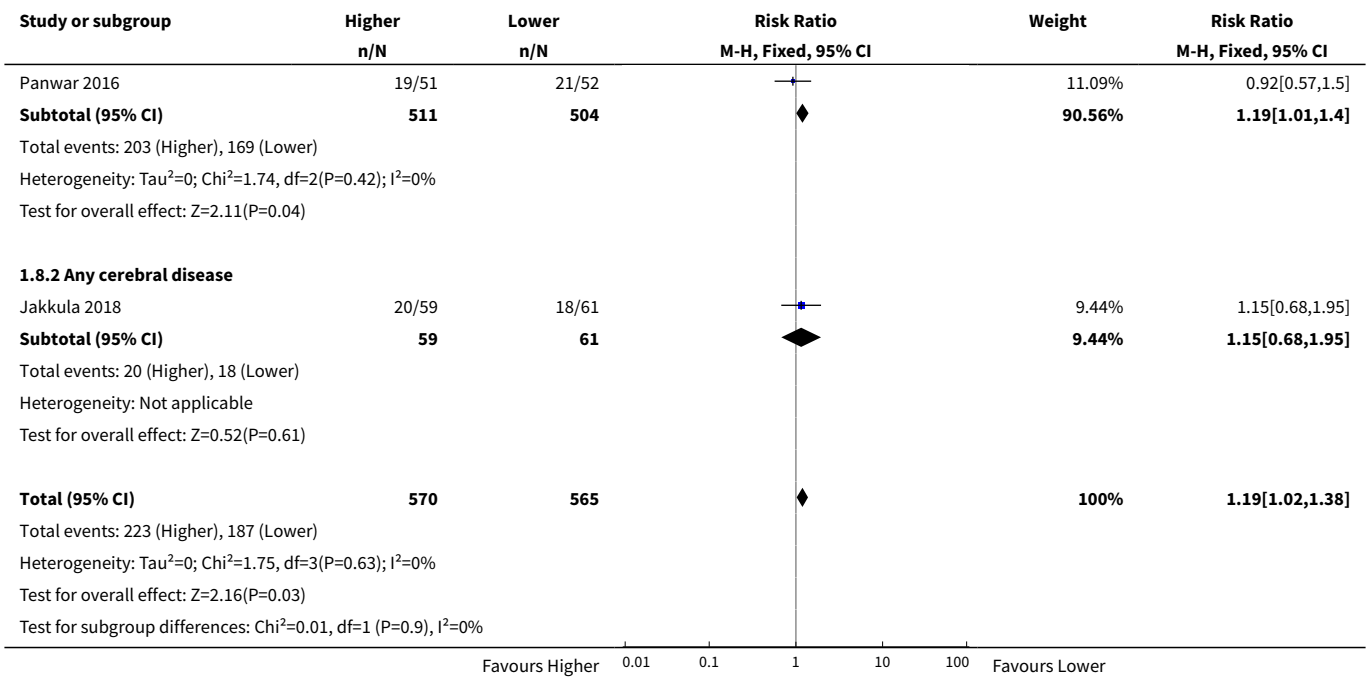


Analysis 1.7. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 7 All-cause mortality - at time point closest to 3 months - level of FiO_2/target in lower group.

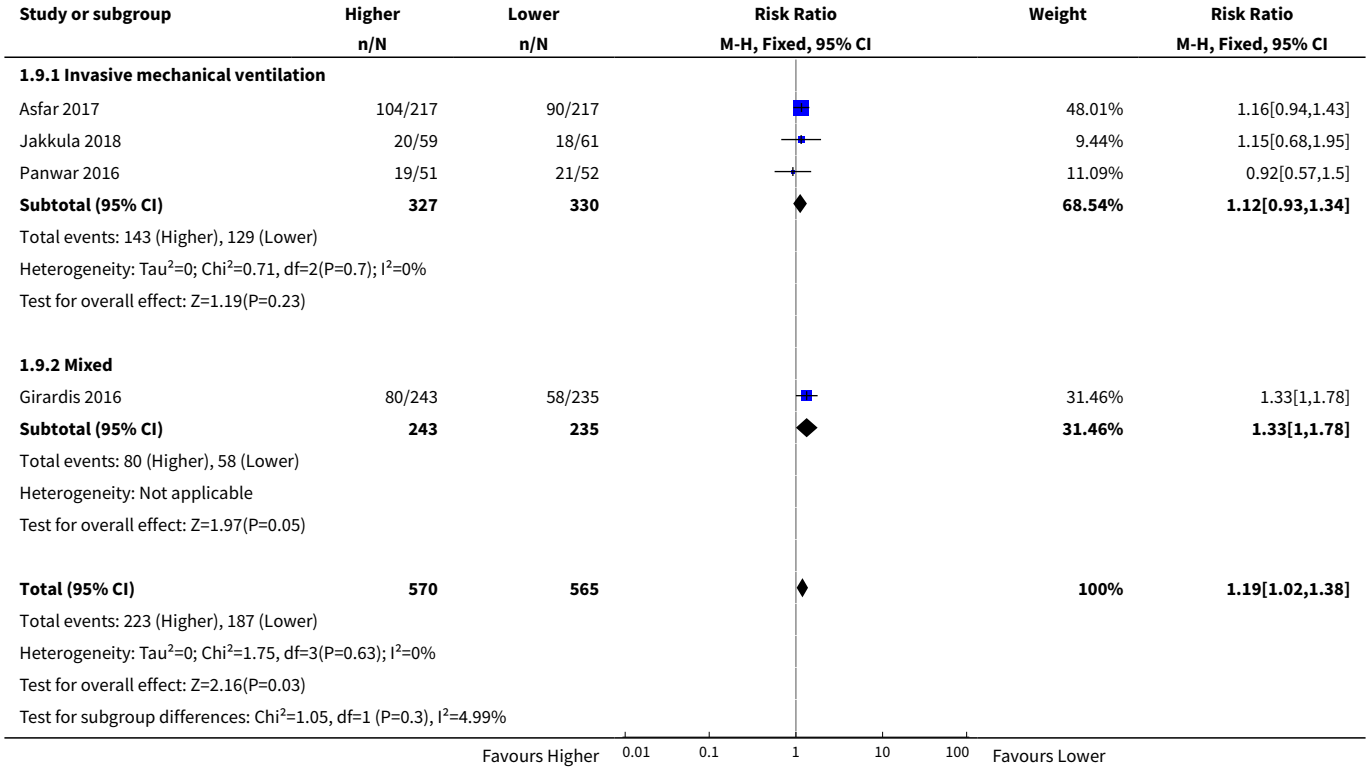


Analysis 1.8. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 8 All-cause mortality - at time point closest to 3 months - ICU population.





Analysis 1.9. Comparison 1 All-cause mortality - at time point closest to 3 months follow-up, Outcome 9 Mortality - at time point closest to 3 months - oxygen delivery system.



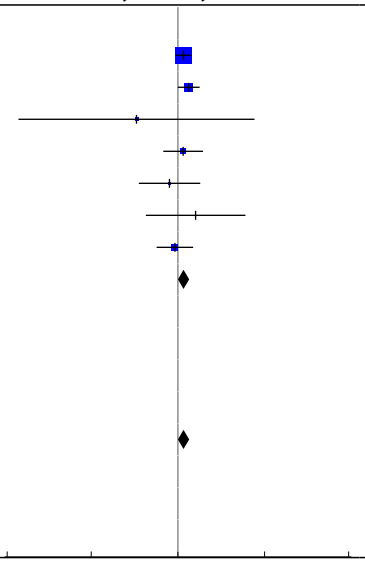
Comparison 2. Sensitivity analysis: all-cause mortality - at maximum follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality - at maximum follow-up	7	1285	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.00, 1.35]
1.1 All-cause mortality	7	1285	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.00, 1.35]
2 Sensitivity analysis: all-cause mortality - at maximum follow-up - high vs high and low vs low excluded	2	537	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.92, 1.35]
3 Sensitivity analysis: all-cause mortality - at maximum follow-up - best-worst-case scenario	7	1306	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.96, 1.28]
3.1 All-cause mortality	7	1306	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.96, 1.28]
4 Sensitivity analysis: all-cause mortality - at maximum follow-up - worst-best-case scenario	7	1306	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.05, 1.41]
4.1 All-cause mortality	7	1306	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.05, 1.41]
5 All-cause mortality - at maximum follow-up - types of oxygen interventions	7	1285	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.00, 1.36]
5.1 PaO_2 (SaO_2 or SpO_2)	4	735	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.96, 1.50]
5.2 FiO_2	2	116	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.50, 1.98]
5.3 Difference between groups	1	434	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.94, 1.43]
6 All-cause mortality - at maximum follow-up - level of FiO_2/target in higher group	7	1285	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.00, 1.36]
6.1 Lower	2	85	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.37, 3.81]
6.2 Higher	5	1200	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.00, 1.36]
7 All-cause mortality - at maximum follow-up - level of FiO_2/target in lower group	7	1285	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.00, 1.36]
7.1 Lower	4	622	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.92, 1.35]
7.2 Higher	3	663	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.97, 1.57]
8 All-cause mortality - at maximum follow-up - ICU population	7	1350	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.99, 1.33]
8.1 Mixed ICU	3	1015	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.01, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Medical ICU	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.65]
8.3 Any trauma	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.35, 1.81]
8.4 Any cerebral disease	3	236	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.71, 1.65]
9 Mortality - at maximum follow-up - oxygen delivery system	7	1285	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.00, 1.36]
9.1 Invasive mechanical ventilation	4	722	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.92, 1.31]
9.2 Any non-invasive oxygen administration	2	85	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.37, 3.81]
9.3 Mixed	1	478	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.00, 1.78]

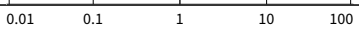
Analysis 2.1. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 1 All-cause mortality - at maximum follow-up.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 All-cause mortality					
Asfar 2017	104/217	90/217		50.46%	1.16[0.94,1.43]
Girardis 2016	80/243	58/235		27.18%	1.33[1,1.78]
Gomersall 2002	0/17	1/17		0.23%	0.33[0.01,7.65]
Jakkula 2018	20/59	18/61		8.04%	1.15[0.68,1.95]
Lång 2018	9/38	8/27		3.36%	0.8[0.35,1.81]
Mazdeh 2015	5/26	3/25		1.28%	1.6[0.43,6.01]
Panwar 2016	19/51	21/52		9.46%	0.92[0.57,1.5]
Subtotal (95% CI)	**651**	**634**		**100%**	**1.16[1,1.35]**
Total events: 237 (Higher), 199 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=3.41, df=6(P=0.76); I^2=0%					
Test for overall effect: Z=1.98(P=0.05)					
Total (95% CI)	**651**	**634**		**100%**	**1.16[1,1.35]**
Total events: 237 (Higher), 199 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=3.41, df=6(P=0.76); I^2=0%					
Test for overall effect: Z=1.98(P=0.05)					



Analysis 2.2. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 2 Sensitivity analysis: all-cause mortality - at maximum follow-up - high vs high and low vs low excluded.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asfar 2017	104/217	90/217		81.23%	1.16[0.94,1.43]
Panwar 2016	19/51	21/52		18.77%	0.92[0.57,1.5]
Total (95% CI)	**268**	**269**		**100%**	**1.11[0.92,1.35]**
Total events: 123 (Higher), 111 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=0.7, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=1.08(P=0.28)					

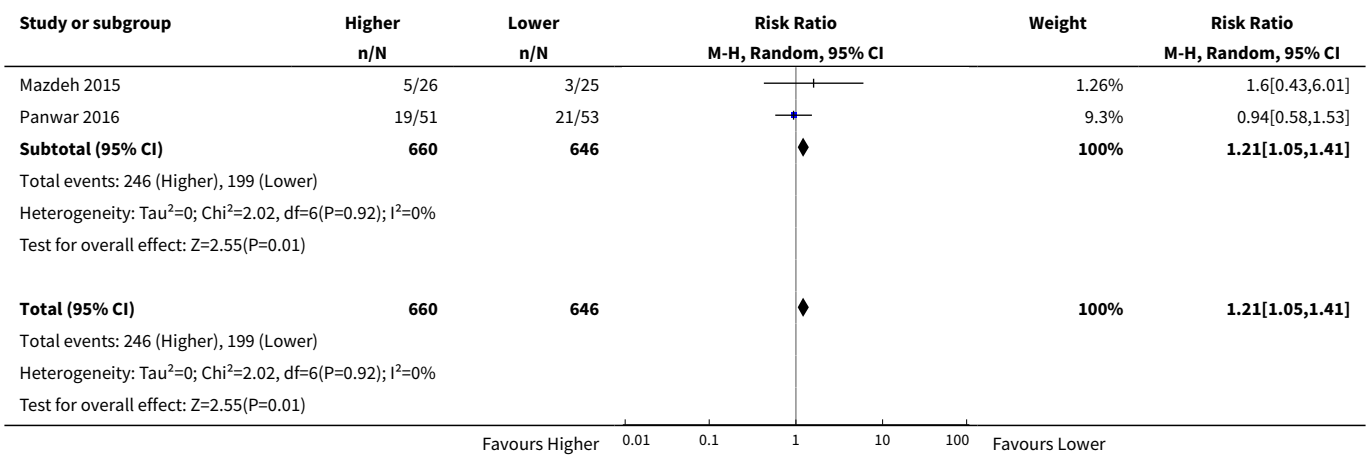


Analysis 2.3. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 3 Sensitivity analysis: all-cause mortality - at maximum follow-up - best-worst-case scenario.

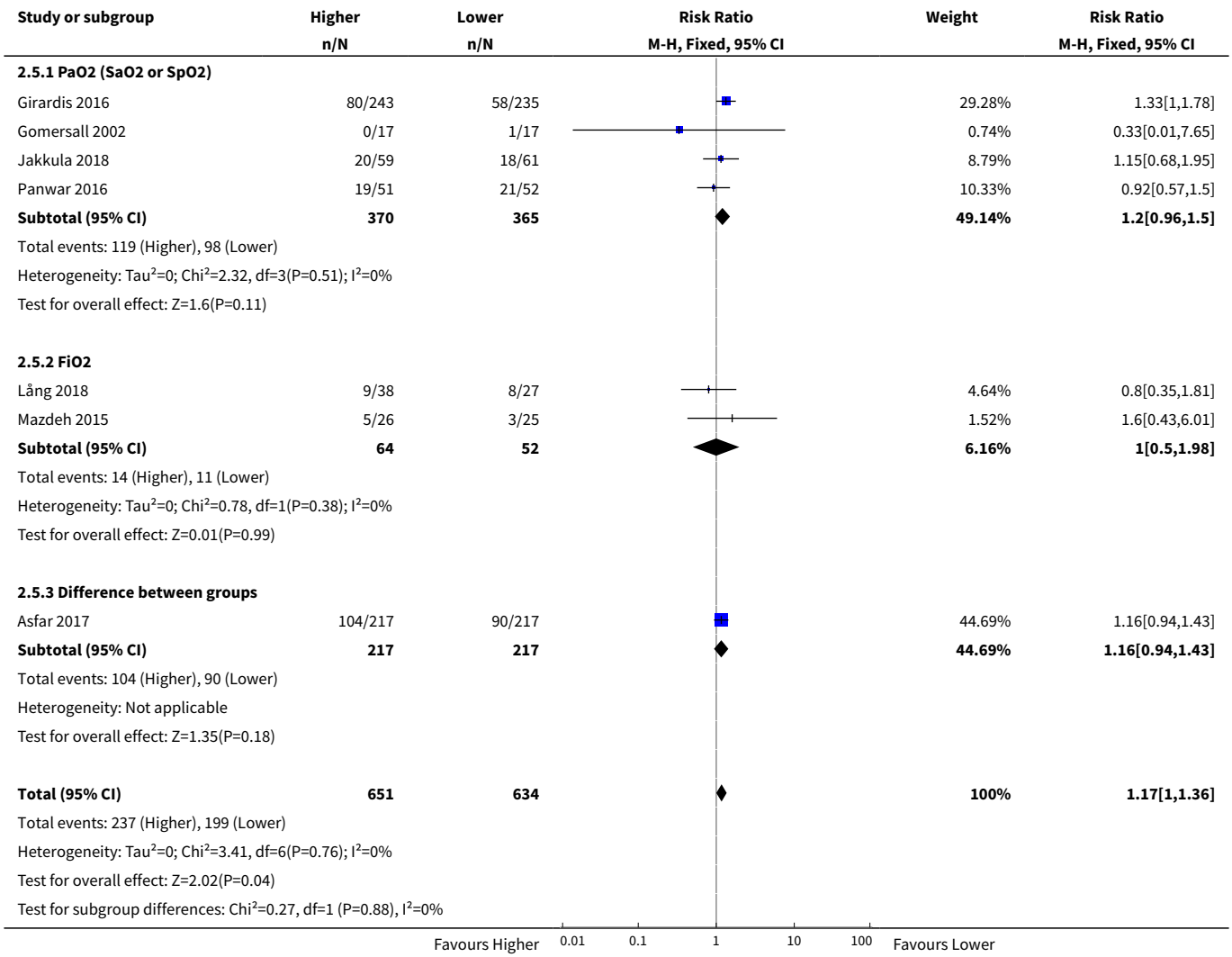
Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 All-cause mortality					
Asfar 2017	104/219	96/223		50.82%	1.1[0.9,1.35]
Girardis 2016	80/244	59/236		26.43%	1.31[0.99,1.74]
Gomersall 2002	0/19	1/17		0.22%	0.3[0.01,6.91]
Jakkula 2018	20/60	20/63		8.27%	1.05[0.63,1.75]
Lång 2018	9/41	10/29		3.67%	0.64[0.3,1.37]
Mazdeh 2015	5/26	3/25		1.23%	1.6[0.43,6.01]
Panwar 2016	19/51	22/53		9.36%	0.9[0.56,1.45]
Subtotal (95% CI)	**660**	**646**		**100%**	**1.11[0.96,1.28]**
Total events: 237 (Higher), 211 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=5.12, df=6(P=0.53); I^2=0%					
Test for overall effect: Z=1.37(P=0.17)					
Total (95% CI)	**660**	**646**		**100%**	**1.11[0.96,1.28]**
Total events: 237 (Higher), 211 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=5.12, df=6(P=0.53); I^2=0%					
Test for overall effect: Z=1.37(P=0.17)					

Analysis 2.4. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 4 Sensitivity analysis: all-cause mortality - at maximum follow-up - worst-best-case scenario.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 All-cause mortality					
Asfar 2017	106/219	90/223		50%	1.2[0.97,1.48]
Girardis 2016	81/244	58/236		27.04%	1.35[1.02,1.8]
Gomersall 2002	2/19	1/17		0.41%	1.79[0.18,18.02]
Jakkula 2018	21/60	18/63		8.14%	1.23[0.73,2.06]
Lång 2018	12/41	8/29		3.85%	1.06[0.5,2.26]



Analysis 2.5. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 5 All-cause mortality - at maximum follow-up - types of oxygen interventions.

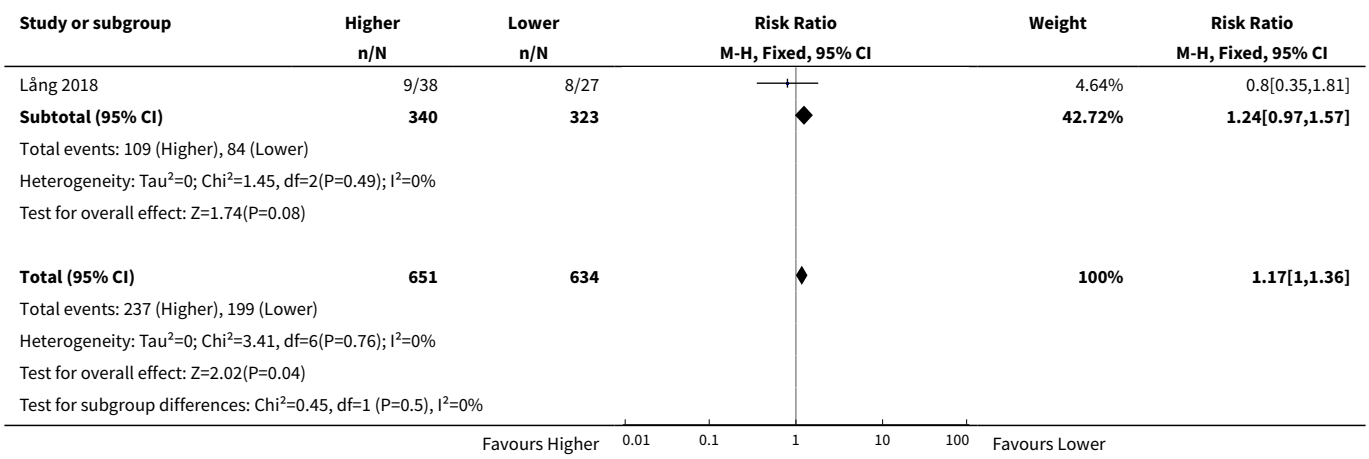


Analysis 2.6. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 6 All-cause mortality - at maximum follow-up - level of FiO_2/target in higher group.

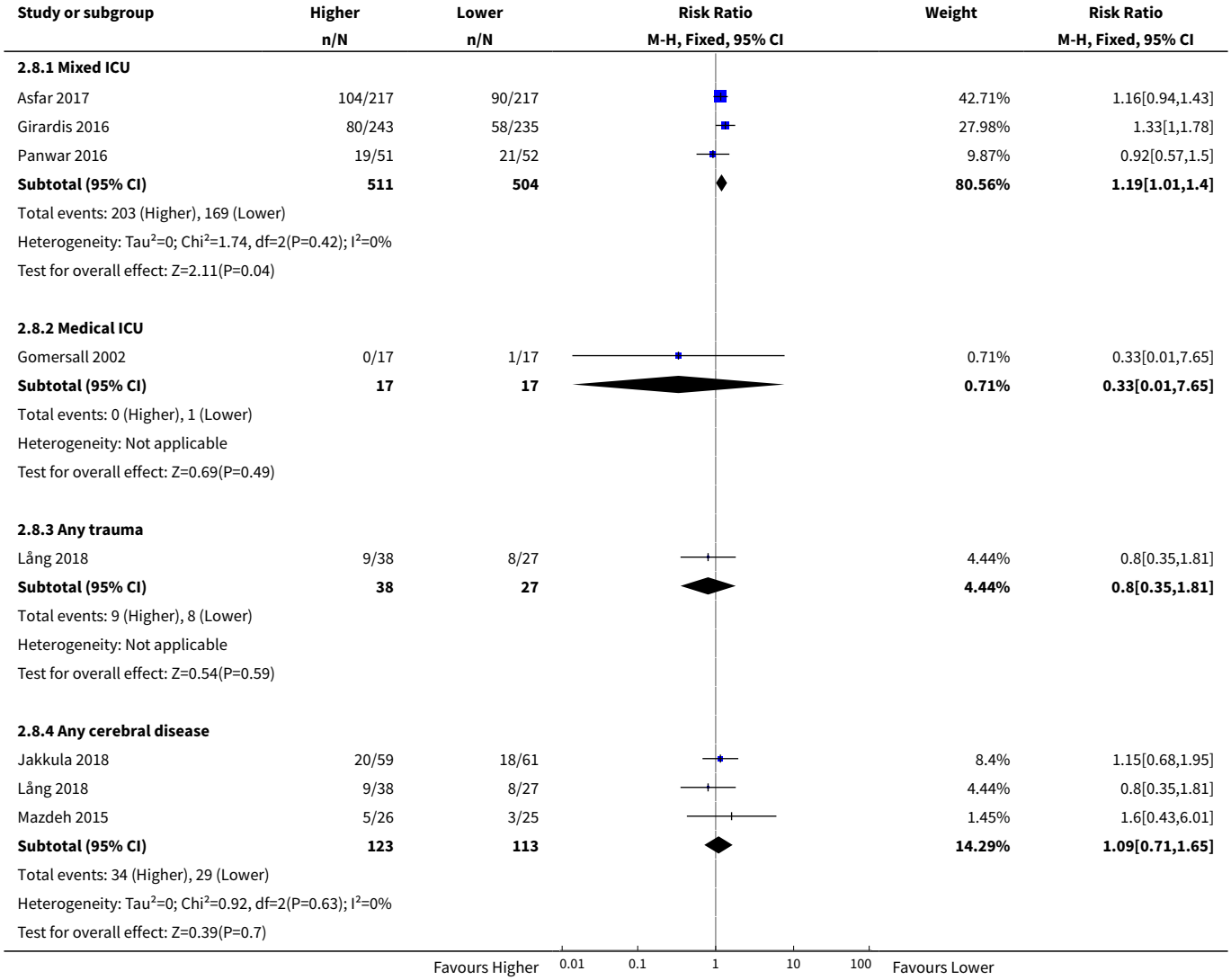
Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Lower					
Gomersall 2002	0/17	1/17		0.74%	0.33[0.01,7.65]
Mazdeh 2015	5/26	3/25		1.52%	1.6[0.43,6.01]
Subtotal (95% CI)	**43**	**42**		**2.26%**	**1.18[0.37,3.81]**
Total events: 5 (Higher), 4 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=0.28(P=0.78)					
2.6.2 Higher					
Asfar 2017	104/217	90/217		44.69%	1.16[0.94,1.43]
Girardis 2016	80/243	58/235		29.28%	1.33[1,1.78]
Jakkula 2018	20/59	18/61		8.79%	1.15[0.68,1.95]
Lång 2018	9/38	8/27		4.64%	0.8[0.35,1.81]
Panwar 2016	19/51	21/52		10.33%	0.92[0.57,1.5]
Subtotal (95% CI)	**608**	**592**		**97.74%**	**1.17[1,1.36]**
Total events: 232 (Higher), 195 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=2.58, df=4(P=0.63); I^2=0%					
Test for overall effect: Z=2(P=0.05)					
Total (95% CI)	**651**	**634**		**100%**	**1.17[1,1.36]**
Total events: 237 (Higher), 199 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=3.41, df=6(P=0.76); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.98), I^2=0%					

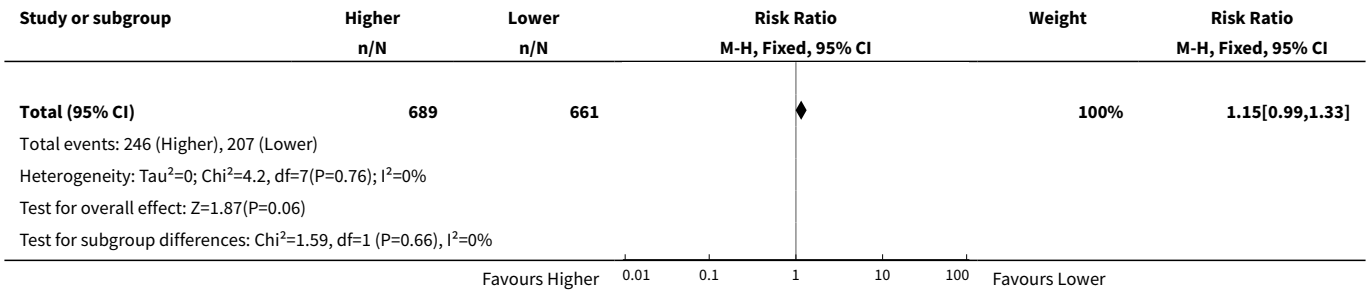
Analysis 2.7. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 7 All-cause mortality - at maximum follow-up - level of FiO_2/target in lower group.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 Lower					
Asfar 2017	104/217	90/217		44.69%	1.16[0.94,1.43]
Gomersall 2002	0/17	1/17		0.74%	0.33[0.01,7.65]
Mazdeh 2015	5/26	3/25		1.52%	1.6[0.43,6.01]
Panwar 2016	19/51	21/52		10.33%	0.92[0.57,1.5]
Subtotal (95% CI)	**311**	**311**		**57.28%**	**1.11[0.92,1.35]**
Total events: 128 (Higher), 115 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=1.56, df=3(P=0.67); I^2=0%					
Test for overall effect: Z=1.11(P=0.27)					
2.7.2 Higher					
Girardis 2016	80/243	58/235		29.28%	1.33[1,1.78]
Jakkula 2018	20/59	18/61		8.79%	1.15[0.68,1.95]

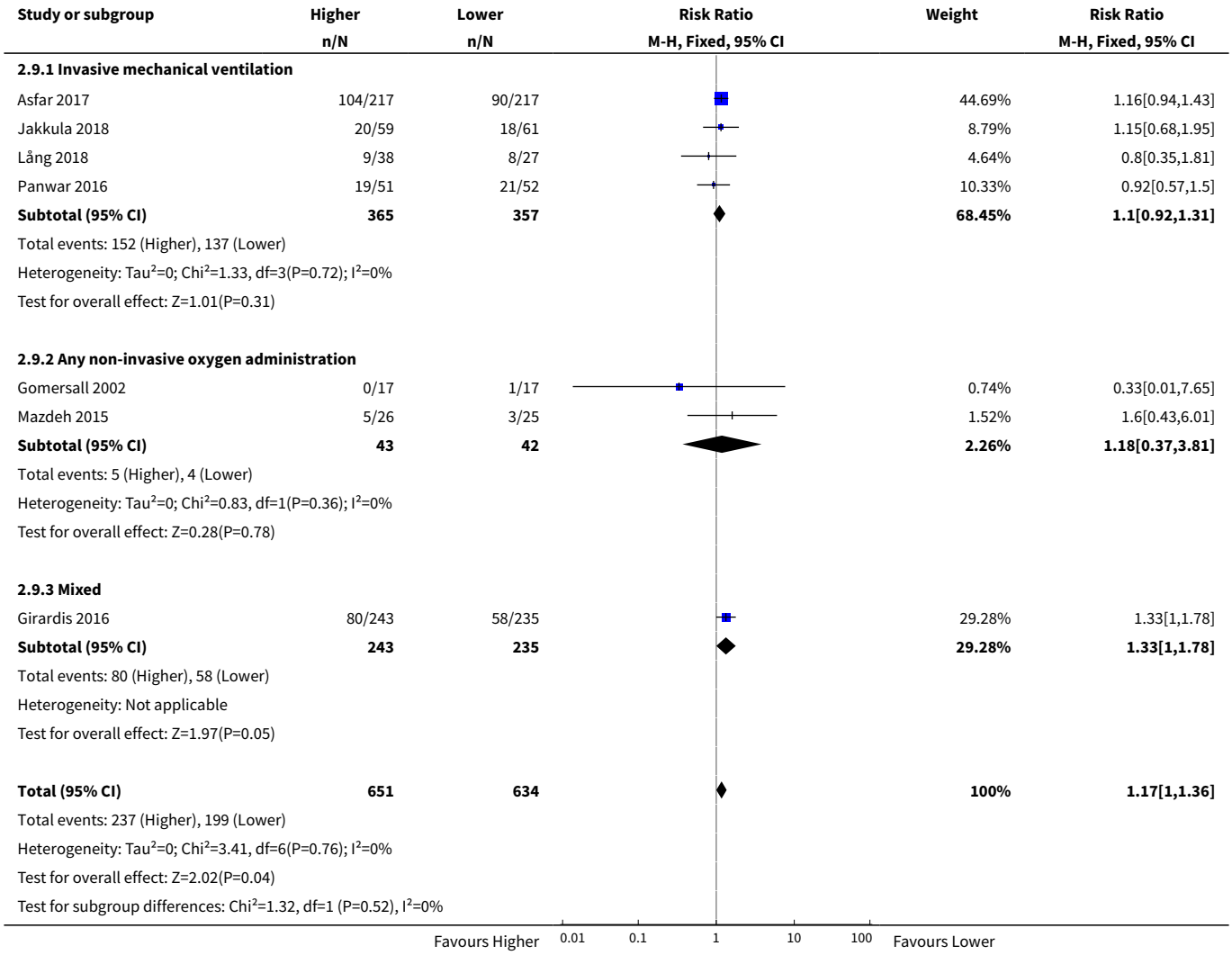


Analysis 2.8. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 8 All-cause mortality - at maximum follow-up - ICU population.





Analysis 2.9. Comparison 2 Sensitivity analysis: all-cause mortality - at maximum follow-up, Outcome 9 Mortality - at maximum follow-up - oxygen delivery system.

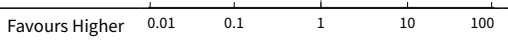


Comparison 3. Serious adverse events - at time point closest to 3 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events - at time point closest to three months - highest proportion	6	1234	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.04, 1.23]
2 Serious adverse events - at time point closest to three months - cumulated	6	1234	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.99, 1.18]

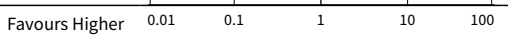
Analysis 3.1. Comparison 3 Serious adverse events - at time point closest to 3 months, Outcome 1 Serious adverse events - at time point closest to three months - highest proportion.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Asfar 2017	185/217	165/217		84.47%	1.12[1.02,1.23]
Girardis 2016	80/243	58/235		8.89%	1.33[1,1.78]
Gomersall 2002	2/17	2/17		0.22%	1[0.16,6.3]
Jakkula 2018	20/59	18/61		2.63%	1.15[0.68,1.95]
Lång 2018	6/38	6/27		0.7%	0.71[0.26,1.97]
Panwar 2016	19/51	21/52		3.09%	0.92[0.57,1.5]
Total (95% CI)	**625**	**609**		**100%**	**1.13[1.04,1.23]**
Total events: 312 (Higher), 270 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=2.88, df=5(P=0.72); I^2=0%					
Test for overall effect: Z=2.78(P=0.01)					



Analysis 3.2. Comparison 3 Serious adverse events - at time point closest to 3 months, Outcome 2 Serious adverse events - at time point closest to three months - cumulated.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Asfar 2017	196/217	186/217		38.06%	1.05[0.98,1.13]
Girardis 2016	243/243	204/235		43.1%	1.15[1.1,1.21]
Gomersall 2002	2/17	2/17		0.22%	1[0.16,6.3]
Jakkula 2018	21/59	21/61		2.97%	1.03[0.63,1.68]
Lång 2018	6/38	9/27		0.89%	0.47[0.19,1.17]
Panwar 2016	42/51	41/52		14.76%	1.04[0.86,1.26]
Total (95% CI)	**625**	**609**		**100%**	**1.08[0.99,1.18]**
Total events: 510 (Higher), 463 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=9.76, df=5(P=0.08); I^2=48.78%					
Test for overall effect: Z=1.85(P=0.07)					

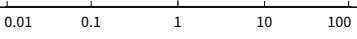


Comparison 4. Sensitivity analysis: serious adverse events - at maximum follow-up

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Serious adverse events - at maximum follow-up - highest proportion	7	1285	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.04, 1.23]
2 Serious adverse events - at maximum follow-up - cumulated	7	1285	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.97, 1.18]

Analysis 4.1. Comparison 4 Sensitivity analysis: serious adverse events - at maximum follow-up, Outcome 1 Serious adverse events - at maximum follow-up - highest proportion.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Asfar 2017	185/217	165/217		83.78%	1.12[1.02,1.23]
Girardis 2016	80/243	58/235		8.82%	1.33[1,1.78]
Gomersall 2002	2/17	2/17		0.21%	1[0.16,6.3]
Jakkula 2018	20/59	18/61		2.61%	1.15[0.68,1.95]
Lång 2018	9/38	8/27		1.09%	0.8[0.35,1.81]
Mazdeh 2015	5/26	3/25		0.41%	1.6[0.43,6.01]
Panwar 2016	19/51	21/52		3.07%	0.92[0.57,1.5]
Total (95% CI)	**651**	**634**		**100%**	**1.13[1.04,1.23]**
Total events: 320 (Higher), 275 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=3.09, df=6(P=0.8); I^2=0%					
Test for overall effect: Z=2.81(P=0)					



Analysis 4.2. Comparison 4 Sensitivity analysis: serious adverse events - at maximum follow-up, Outcome 2 Serious adverse events - at maximum follow-up - cumulated.

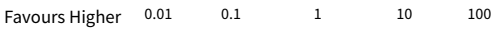
Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Asfar 2017	196/217	186/217		36.18%	1.05[0.98,1.13]
Girardis 2016	243/243	204/235		39.86%	1.15[1.1,1.21]
Gomersall 2002	2/17	3/17		0.33%	0.67[0.13,3.5]
Jakkula 2018	21/59	21/61		3.51%	1.03[0.63,1.68]
Lång 2018	15/38	17/27		3.49%	0.63[0.38,1.02]
Mazdeh 2015	5/26	3/25		0.51%	1.6[0.43,6.01]
Panwar 2016	42/51	41/52		16.12%	1.04[0.86,1.26]
Total (95% CI)	**651**	**634**		**100%**	**1.07[0.97,1.18]**
Total events: 524 (Higher), 475 (Lower)					
Heterogeneity: Tau^2=0.01; Chi^2=12.57, df=6(P=0.05); I^2=52.25%					
Test for overall effect: Z=1.41(P=0.16)					

Comparison 5. Lung injury - at time point closest to 3 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lung injury - at time point closest to three months - highest proportion	5	1167	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.78, 1.36]
2 Lung injury - at time point closest to three months - cumulated	5	1167	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.75, 1.30]
3 Lung injury - at time point closest to three months - ARDS	3	288	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.28, 2.20]
4 Lung injury - at time point closest to three months - pneumonia	3	944	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.40]

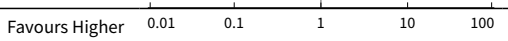
Analysis 5.1. Comparison 5 Lung injury - at time point closest to 3 months, Outcome 1 Lung injury - at time point closest to three months - highest proportion.

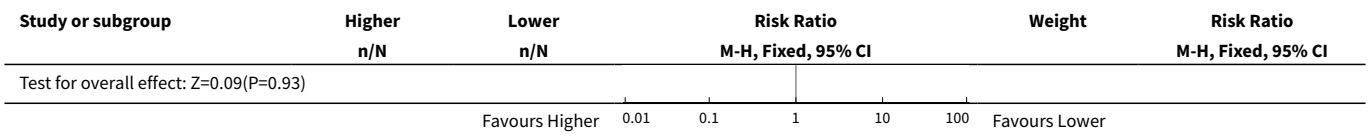
Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asfar 2017	30/217	32/217		39.39%	0.94[0.59,1.49]
Girardis 2016	37/225	30/220		37.35%	1.21[0.77,1.88]
Jakkula 2018	1/59	1/61		1.21%	1.03[0.07,16.15]
Lång 2018	6/38	6/27		8.64%	0.71[0.26,1.97]
Panwar 2016	11/51	11/52		13.41%	1.02[0.49,2.14]
Total (95% CI)	**590**	**577**		**100%**	**1.03[0.78,1.36]**
Total events: 85 (Higher), 80 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=1.16, df=4(P=0.89); I^2=0%					
Test for overall effect: Z=0.21(P=0.83)					



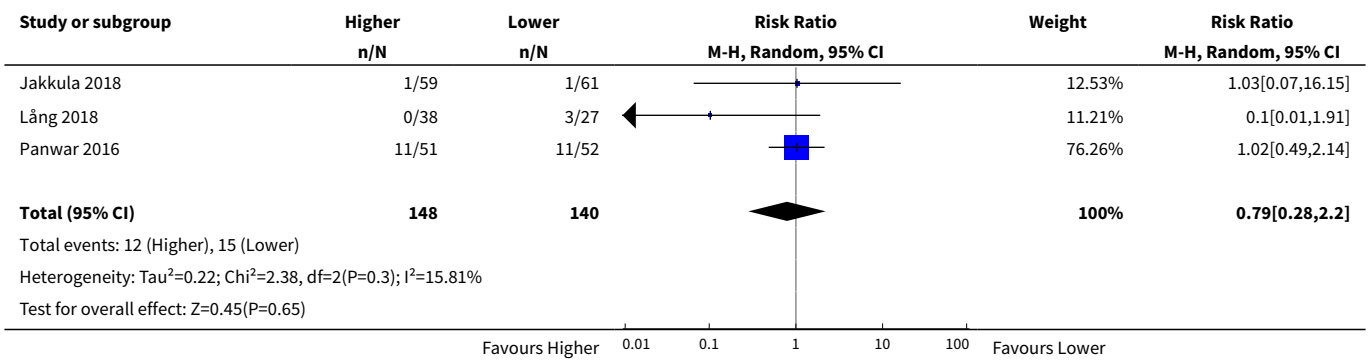
Analysis 5.2. Comparison 5 Lung injury - at time point closest to 3 months, Outcome 2 Lung injury - at time point closest to three months - cumulated.

Study or subgroup	Higher n/N	Lower n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asfar 2017	30/217	32/217		37.76%	0.94[0.59,1.49]
Girardis 2016	37/225	30/220		35.8%	1.21[0.77,1.88]
Jakkula 2018	1/59	1/61		1.16%	1.03[0.07,16.15]
Lång 2018	6/38	9/27		12.42%	0.47[0.19,1.17]
Panwar 2016	11/51	11/52		12.86%	1.02[0.49,2.14]
Total (95% CI)	**590**	**577**		**100%**	**0.99[0.75,1.3]**
Total events: 85 (Higher), 83 (Lower)					
Heterogeneity: Tau^2=0; Chi^2=3.35, df=4(P=0.5); I^2=0%					

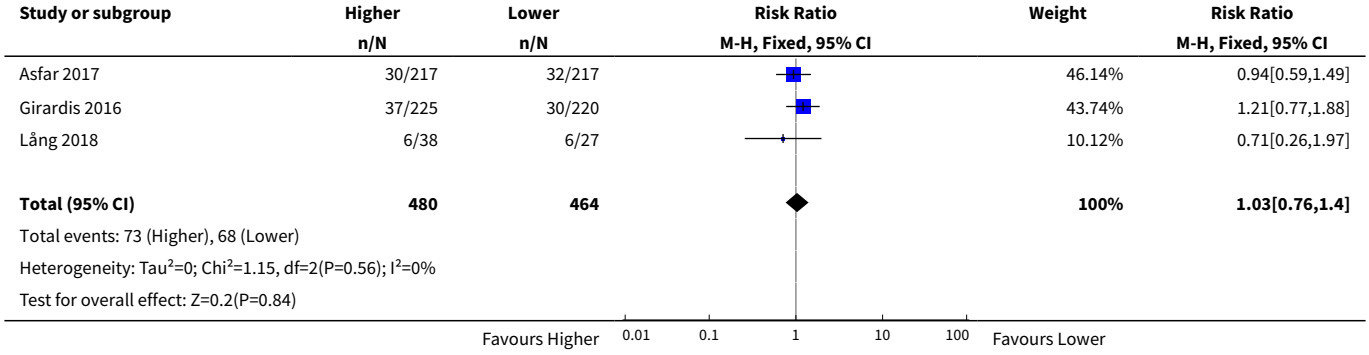




Analysis 5.3. Comparison 5 Lung injury - at time point closest to 3 months, Outcome 3 Lung injury - at time point closest to three months - ARDS.



Analysis 5.4. Comparison 5 Lung injury - at time point closest to 3 months, Outcome 4 Lung injury - at time point closest to three months - pneumonia.



ADDITIONAL TABLES

Table 1. Interventions used in the higher and lower group

	Higher group			Lower group		
	FiO_2	PaO_2	SaO_2/SpO_2	FiO_2	PaO_2	SaO_2/SpO_2
Asfar 2017	1.00	-	-	-	-	88% to 95%
Girardis 2016	≥ 0.40	≤ 20 kPa (150 mmHg)	97% to 100%	-	9.3 to 13.3 kPa (70 to 100 mmHg)	94% to 98%

Table 1. Interventions used in the higher and lower group *(Continued)*

Gomersall 2002	-	> 9.0 kPa (67.5 mmHg)	-	-	> 6.6 kPa (50 mmHg)	-
Ishii 2018	1.00	-	-	-	100 mmHg (13.3 kPa)	-
Jakkula 2018	-	20 to 25 kPa (150 to 187.5 mmHg)	-	-	10 to 15 kPa (75 to 112.5 mmHg)	95% to 98%
Lång 2018	0.70	-	-	0.40	-	-
Mazdeh 2015	0.50	-	-	Supplemental oxygen not used		
Panwar 2016	-	-	≥ 96%	-	-	88% to 92%
Taher 2016	0.80	-	-	0.50	-	-
Young 2017	No specific measures taken to avoid high FiO_2 or SpO_2, FiO_2 < 0.30 discouraged.			-	-	91% to 96%

FiO_2: fraction of inspired oxygen; **PaO_2**: partial pressure of arterial oxygen; **SaO_2**: arterial oxygen saturation of haemoglobin; **SpO_2**: peripheral oxygen saturation

Table 2. Calculated Bayes factors for the primary outcomes

Outcome	Intervention effect hypothesised	Intervention effect shown by the meta-analysis	Bayes factor (BF)	Interpretation
Mortality *Time point closest to 3 months*	RR 0.80	RR 1.18	18078	*
Mortality *Time point closest to 3 months*	RR 1.20	RR 1.18	0.12 (BF^{-1} = 8.3)	**
Mortality *Maximum follow-up*	RR 0.80	RR 1.16	12867	*
Mortality *Maximum follow-up*	RR 1.20	RR 1.16	0.18 (BF^{-1} = 5.6)	**
Estimated highest reported proportion of serious adverse events *Time point closest to 3 months*	RR 0.80	RR 1.13	2114269	*
Estimated highest reported proportion of serious adverse events *Time point closest to 3 months*	RR 1.20	RR 1.13	0.21 (BF^{-1} = 4.8)	**
Estimated cumulated number of serious adverse events	RR 0.80	RR 1.08	$6.2*10^{20}$	*

Table 2. Calculated Bayes factors for the primary outcomes *(Continued)*

Time point closest to 3 months				
Estimated cumulated number of serious adverse events *Time point closest to 3 months*	RR 1.20	RR 1.08	19 (BF^{-1} = 0.05)	**
Estimated highest reported proportion of serious adverse events *Maximum follow-up*	RR 0.80	RR 1.13	1624463	*
Estimated highest reported proportion of serious adverse events *Maximum follow-up*	RR 1.20	RR 1.13	0.21 (BF^{-1} = 4.8)	**
Estimated cumulated number of serious adverse events *Maximum follow-up*	RR 0.80	RR 1.07	$1.96*10^{19}$	*
Estimated cumulated number of serious adverse events *Maximum follow-up*	RR 1.20	RR 1.07	117 (BF^{-1} = 0.01)	**

Abbreviations: **RR:** risk ratio
*The result is likely BF times more compatible with the null-hypothesis of a relative risk reduction of 0% than the alternative hypothesis of a relative risk reduction of 20% for an effect of higher versus lower supplemental oxygen on all-cause mortality.
**The result is likely BF^{-1} times more compatible with the alternative hypothesis of a relative risk increase of 20% than the null-hypothesis of a relative risk increase of 0% for an effect of higher versus lower supplemental oxygen on all-cause mortality.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Hyperoxia] explode all trees
#2 MeSH descriptor: [Anoxia] explode all trees
#3 MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees
#4 MeSH descriptor: [Oxygen] explode all trees
#5 (inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) near/3 (oxygen):ti,ab,kw
#6 (hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2):ti,ab,kw
#7 (#1 or #2 or #3 or #4 or #5 or #6)
#8 MeSH descriptor: [Critical Illness] explode all trees
#9 MeSH descriptor: [Critical Care] explode all trees
#10 MeSH descriptor: [Intensive Care Units] explode all trees
#11 MeSH descriptor: [Emergency Medicine] explode all trees
#12 MeSH descriptor: [Emergency Service, Hospital] explode all trees
#13 (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU* or coronary care unit or neurological intermediate care unit):ti,ab,kw
#14 MeSH descriptor: [Heart Arrest] explode all trees
#15 MeSH descriptor: [Myocardial Ischemia] explode all trees
#16 (cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct* or myocardial ischemia or acute coronary syndrome):ti,ab,kw
#17 MeSH descriptor: [Shock] explode all trees
#18 (shock):ti,ab,kw
#19 MeSH descriptor: [Meningitis] explode all trees
#20 (meningitis):ti,ab,kw
#21 MeSH descriptor: [Pneumonia] explode all trees
#22 (pneumonia):ti,ab,kw

#23 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
#24 (COPD or chronic obstructive pulmonary disease):ti,ab,kw
#25 MeSH descriptor: [Acute Lung Injury] explode all trees
#26 (acute lung injury):ti,ab,kw
#27 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees
#28 (adult respiratory distress syndrome or ARDS):ti,ab,kw
#29 MeSH descriptor: [Pulmonary Embolism] explode all trees
#30 (pulmonary embolism or pulmonary infarct*):ti,ab,kw
#31 MeSH descriptor: [Multiple Trauma] explode all trees
#32 (severe trauma or multiple trauma):ti,ab,kw
#33 MeSH descriptor: [Craniocerebral Trauma] explode all trees
#34 (traumatic brain injury or TBI or head trauma or craniocerebral trauma):ti,ab,kw
#35 MeSH descriptor: [Stroke] explode all trees
#36 (stroke):ti,ab,kw
#37 MeSH descriptor: [Sepsis] explode all trees
#38 MeSH descriptor: [Shock, Septic] explode all trees
#39 (sepsis or septic shock):ti,ab,kw
#40 MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#41 intracranial hemorrhage or subarachnoid hemorrhage or cerebral hemorrhage or intracranial bleeding or life-threatening bleeding:ti,ab,kw
#42 MeSH descriptor: [Poisoning] explode all trees
#43 (severe poisoning):ti,ab,kw
#44 MeSH descriptor: [Diabetic Ketoacidosis] explode all trees
#45 (diabetic ketoacidosis):ti,ab,kw
#46 MeSH descriptor: [Liver Failure, Acute] explode all trees
#47 (acute hepatic failure or fulminating hepatic failure):ti,ab,kw
#48 MeSH descriptor: [Acute Kidney Injury] explode all trees
#49 (acute kidney failure or acute renal injuries):ti,ab,kw
#50 MeSH descriptor: [Intestinal Perforation] explode all trees
#51 MeSH descriptor: [Appendicitis] explode all
#52 (intestinal perforation or appendicitis):ti,ab,kw
#53 (acute or emergency) near/2 (surgery or operat* or resection):ti,ab,kw
#54 (#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53)
#55 (#7 and #54)

Appendix 2. MEDLINE (OvidSP) search strategy

1. exp Hyperoxia/
2. exp Anoxia/
3. exp Oxygen Inhalation Therapy/
4. exp Oxygen/
5. ((inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) adj3 oxygen).tw.
6. (hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2).tw.
7. (1 or 2 or 3 or 4 or 5 or 6)
8. exp Critical Illness/
9. exp Critical Care/
10. exp Intensive Care Units/
11. exp Emergency Medicine/
12. exp Emergency Service, Hospital/
13. (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU* or coronary care unit or neurological intermediate care unit).tw.
14. exp Heart Arrest/
15. exp Myocardial Ischemia/
16. (cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct* or myocardial ischemia or acute coronary syndrome).tw.
17. exp Shock/
18. shock.tw.
19. exp Meningitis/

20. meningitis.tw.
21. exp Pneumonia/
22. pneumonia.tw.
23. exp Pulmonary Disease, Chronic Obstructive/
24. (COPD or chronic obstructive pulmonary disease).tw.
25. exp Acute Lung Injury/
26. acute lung injury.tw.
27. exp Respiratory Distress Syndrome, Adult/
28. (adult respiratory distress syndrome or ARDS).tw.
29. exp Pulmonary Embolism/
30. (pulmonary embolism or pulmonary infarct*).tw.
31. exp Multiple Trauma/
32. (severe trauma or multiple trauma).tw.
33. exp Craniocerebral Trauma/
34. (traumatic brain injury or TBI or head trauma or craniocerebral trauma).tw.
35. exp Stroke/
36. stroke.tw.
37. exp Sepsis/
38. exp Shock, Septic/
39. (sepsis or septic shock).tw.
40. exp Intracranial Hemorrhages/
41. (intracranial hemorrhage or subarachnoid hemorrhage or cerebral hemorrhage or intracranial bleeding or life-threatening bleeding).tw.
42. exp Poisoning/
43. severe poisoning.tw.
44. exp Diabetic Ketoacidosis/
45. diabetic ketoacidosis.tw.
46. exp Liver Failure, Acute/
47. (acute hepatic failure or fulminating hepatic failure).tw.
48. exp Acute Kidney Injury/
49. (acute kidney failure or acute renal injuries).tw.
50. exp Intestinal Perforation/
51. exp Appendicitis/
52. (intestinal perforation or appendicitis).tw.
53. ((acute or emergency) adj2 (surgery or operat* or resection)).tw.
54. (8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53)
55. (7 and 54)
56. randomized controlled trial.pt.
57. controlled clinical trial.pt.
58. randomized.ab.
59. placebo.ab.
60. clinical trial.sh.
61. randomly.ab.
62. trial.ti.
63. (56 or 57 or 58 or 59 or 60 or 61 or 62)
64. exp animals/not humans.sh.
65. (63 not 64)
66. (55 and 65)

Appendix 3. Embase (OvidSP) search strategy

1. *hyperoxia/
2. *hypoxia/
3. *oxygen therapy/
4. *oxygen/
5. *arterial oxygen saturation/
6. *oxygen blood level/
7. *arterial oxygen tension/
8. *blood oxygen tension/
9. ((inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) adj3 oxygen).tw.

10. (hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2).tw.
11. (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10)
12. *critical illness/
13. *intensive care/
14. *intensive care unit/
15. *emergency medicine/
16. *emergency health service/
17. *coronary care unit/
18. (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU* or coronary care unit or neurological intermediate care unit).tw.
19. *heart arrest/
20. *acute heart infarction/
21. (cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct* or myocardial ischemia or acute coronary syndrome).tw.
22. *shock/
23. shock.tw.
24. *meningitis/
25. meningitis.tw.
26. *pneumonia/
27. pneumonia.tw.
28. *chronic obstructive lung disease/
29. (COPD or chronic obstructive pulmonary disease).tw.
30. *acute lung injury/
31. acute lung injury.tw.
32. *adult respiratory distress syndrome/
33. (adult respiratory distress syndrome or ARDS).tw.
34. *lung embolism/
35. (pulmonary embolism or pulmonary infarct*).tw.
36. *multiple trauma/
37. (severe trauma or multiple trauma).tw.
38. *head injury/
39. *brain injury/
40. (traumatic brain injury or TBI or head trauma or craniocerebral trauma).tw.
41. *cerebrovascular accident/
42. *stroke unit/
43. stroke.tw.
44. *sepsis/
45. *septic shock/
46. (sepsis or septic shock).tw.
47. *brain hemorrhage/
48. (intracranial hemorrhage or subarachnoid hemorrhage or cerebral hemorrhage or intracranial bleeding or life-threatening bleeding).tw.
49. *intoxication/
50. severe poisoning.tw.
51. *diabetic ketoacidosis/
52. diabetic ketoacidosis.tw.
53. *acute liver failure/
54. (acute hepatic failure or fulminating hepatic failure).tw.
55. *acute kidney failure/
56. (acute kidney failure or acute renal injuries).tw.
57. *intestine perforation/
58. *appendicitis/
59. (intestinal perforation or appendicitis).tw.
60. ((acute or emergency) adj2 (surgery or operat* or resection)).tw.
61. (12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60)
62. (11 and 61)
63. CROSSOVER PROCEDURE.sh.
64. DOUBLE-BLIND PROCEDURE.sh.
65. SINGLE-BLIND PROCEDURE.sh.
66. (crossover* or cross over*).ti,ab.

67. placebo*.ti,ab.
68. (doubl* adj blind*).ti,ab.
69. allocat*.ti,ab.
70. trial.ti.
71. RANDOMIZED CONTROLLED TRIAL.sh.
72. random*.ti,ab.
73. (63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72)
74. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)
75. (73 not 74)
76. (62 and 75)

Appendix 4. Science Citation Index - Expanded search strategy

#27 (#26 AND #25)
#26 TOPIC: (((random* OR control* OR RCT OR placebo OR group* OR trial*)))
#25 (#24 AND #3)
#24 (#23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4)
#23 TITLE: (((acute or emergency) and (surgery or operat* or resection)))
#22 TOPIC: ((intestinal perforation or appendicitis))
#21 TOPIC: ((acute kidney failure or acute renal injuries))
#20 TOPIC: ((acute hepatic failure or fulminating hepatic failure))
#19 TOPIC: ((diabetic ketoacidosis))
#18 TOPIC: ((severe poisoning))
#17 TOPIC: ((intracranial hemorrhage or subarachnoid hemorrhage or cerebral hemorrhage or intracranial bleeding or life-threatening bleeding))
#16 TOPIC: ((sepsis or septic shock))
#15 TOPIC: (stroke)
#14 TOPIC: ((traumatic brain injury or TBI or head trauma or craniocerebral trauma))
#13 TOPIC: ((severe trauma or multiple trauma))
#12 TOPIC: ((pulmonary embolism or pulmonary infarct*))
#11 TOPIC: ((adult respiratory distress syndrome or ARDS))
#10 TOPIC: (acute lung injury)
#9 TOPIC: ((COPD or chronic obstructive pulmonary disease))
#8 TOPIC: (pneumonia)
#7 TOPIC: (meningitis)
#6 TOPIC: (shock)
#5 TOPIC: ((cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct* or myocardial ischemia or acute coronary syndrome))
#4 TOPIC: ((emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU* or coronary care unit or neurological intermediate care unit))
#3 (#2 OR #1)
#2 TITLE: (((hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2)))
#1 TITLE: ((((inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) and oxygen)))

Appendix 5. BIOSIS Previews search strategy

#27 (#26 AND #25)
#26 TOPIC: ((random* OR control* OR RCT OR placebo OR group* OR trial*))
#25 (#24 AND #3)
#24 (#23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4)
#23 TITLE: ((((acute or emergency) and (surgery or operat* or resection))))
#22 TOPIC: (((intestinal perforation or appendicitis)))
#21 TOPIC: (((acute kidney failure or acute renal injuries)))
#20 TOPIC: (((acute hepatic failure or fulminating hepatic failure)))
#19 TOPIC: (((diabetic ketoacidosis)))
#18 TOPIC: (((severe poisoning)))
#17 TOPIC: (((intracranial hemorrhage or subarachnoid hemorrhage or cerebral hemorrhage or intracranial bleeding or life-threatening bleeding)))

#16 TOPIC: (((sepsis or septic shock)))
#15 TOPIC: ((stroke))
#14 TOPIC: (((traumatic brain injury or TBI or head trauma or craniocerebral trauma)))
#13 TOPIC: (((severe trauma or multiple trauma)))
#12 TOPIC: (((pulmonary embolism or pulmonary infarct*)))
#11 TOPIC: (((adult respiratory distress syndrome or ARDS)))
#10 TOPIC: ((acute lung injury))
#9 TOPIC: (((COPD or chronic obstructive pulmonary disease)))
#8 TOPIC: ((pneumonia))
#7 TOPIC: ((meningitis))
#6 TOPIC: ((shock))
#5 TOPIC: (((cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct* or myocardial ischemia or acute coronary syndrome)))
#4 TOPIC: (((emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU* or coronary care unit or neurological intermediate care unit)))
#3 (#2 OR #1)
#2 TITLE: (((hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2)))
#1 TITLE: (((inspir* or inhal* or fraction* or concentrat* or arterial* or saturation or level* or tension* or supply* or supplement* or supplie* or therap* or administr* or dosag* or dose* or dosing*) and oxygen))

Appendix 6. CINAHL search strategy

S66 (S53 AND S65)
S65 (S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64)
S64 TX allocat* random*
S63 (MH "Quantitative Studies")
S62 (MH "Placebos")
S61 TX placebo*
S60 TX random* allocat*
S59 (MH "Random Assignment")
S58 TX randomi* control* trial*
S57 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S56 TX clinic* n1 trial*
S55 PT Clinical trial
S54 (MH "Clinical Trials+")
S53 (S7 AND S52)
S52 (S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51)
S51 AB ((acute or emergency)) AND AB ((surgery or operat* or resection))
S50 AB (intestinal perforation or appendicitis)
S49 MW Appendicitis
S48 MW Intestinal Perforation
S47 AB (acute kidney failure or acute renal injuries)
S46 MW acute kidney failure
S45 AB (acute hepatic failure or fulminating hepatic failure)
S44 MW Liver Failure, Acute
S43 AB diabetic ketoacidosis
S42 MW Diabetic Ketoacidosis
S41 AB severe poisoning
S40 MW Poisoning
S39 AB (intracranial hemorrhage or subarachnoid hemorrhage or cerebral hemorrhage or intracranial bleeding or life-threatening bleeding)
S38 MW Intracranial Hemorrhage
S37 AB (sepsis or septic shock)
S36 MW Shock, Septic
S35 MW Sepsis
S34 AB stroke
S33 MW Stroke
S32 AB (traumatic brain injury or TBI or head trauma or craniocerebral trauma)

S31 AB (severe trauma or multiple trauma)
S30 MW Multiple Trauma
S29 AB (pulmonary embolism or pulmonary infarct*)
S28 MW Pulmonary Embolism
S27 AB (adult respiratory distress syndrome or ARDS)
S26 MW Respiratory Distress Syndrome
S25 AB acute lung injury
S24 MW Acute Lung Injury
S23 MW (COPD or chronic obstructive pulmonary disease)
S22 MW Pulmonary Disease, Chronic Obstructive
S21 AB pneumonia
S20 MW Pneumonia
S19 AB meningitis
S18 MW Meningitis
S17 AB shock
S16 MW Shock
S15 AB (cardiac arrest or cardiac failure or CPR or heart arrest or heart failure or myocardial infarct* or myocardial ischemia or acute coronary syndrome)
S14 MW Myocardial Ischemia
S13 MW heart arrest
S12 AB (emergency department*) or (ED) or (emergency room*) or (ER) or (high dependency unit*) or (HDU) or (prehospital*) or (critically ill) or (acutely ill) or (intensive care) or (critical care) or (ICU*) or (coronary care unit) or (neurological intermediate care unit)
S11 MW emergency medicine
S10 MW intensive care units
S9 MW critical care
S8 MW critical illness
S7 (S1 OR S2 OR S3 OR S4 OR S5 OR S6)
S6 AB (hyperoxia) or (hyperoxemia) or (hyperoxaemia) or (hypoxia) or (hypoxemia) or (hypoxaemia) or (anoxia) or (anoxemia) or (anoxaemia) or (arterial oxygen) or (high oxygen) or (oxygenat*) or (blood gas) or (oxygen saturation) or (pao2) or (sao2) or (spo2) or (fio2)
S5 AB (((inspir*) or (inhal*) or (fraction*) or (concentrat*) or (arterial*) or (saturation) or (level*) or (tension*) or (supply*) or (supplement*) or (supplie*) or (therap*) or (administr*) or (dosag*) or (dose*) or (dosing*))) AND AB (oxygen)
S4 MW oxygen
S3 MW oxygen therapy
S2 MW anoxia
S1 MW hyperoxia

Appendix 7. LILACS search strategy

(tw:((hyperoxia OR hyperoxemia OR hyperoxaemia OR hypoxia OR hypoxemia OR hypoxaemia OR anoxia OR anoxemia OR anoxaemia OR oxygenation OR oxygen OR pao2 OR sao2 OR spo2 OR fio2))) AND (tw:((acute surgery OR acute operation OR acute resection OR emergency surgery OR emergency operation OR emergency resection) OR (intestinal perforation OR appendicitis) OR (acute kidney failure OR acute renal injuries) OR (acute hepatic failure OR fulminating hepatic failure) OR (diabetic ketoacidosis) OR (severe poisoning) OR (intracranial hemorrhage OR subarachnoid hemorrhage OR cerebral hemorrhage OR intracranial bleeding OR life-threatening bleeding) OR (sepsis OR septic shock) OR (stroke) OR (traumatic brain injury OR tbi OR head trauma OR craniocerebral trauma) OR (severe trauma OR multiple trauma) OR (pulmonary embolism OR pulmonary infarction) OR (adult respiratory distress syndrome OR ards) OR (acute lung injury) OR (copd OR chronic obstructive pulmonary disease) OR (pneumonia) OR (meningitis) OR (shock) OR (cardiac arrest OR cardiac failure OR cpr OR heart arrest OR heart failure OR myocardial infarction OR myocardial ischemia OR acute coronary syndrome) OR (emergency department OR ed OR emergency room OR er OR high dependency unit OR hdu OR prehospital OR critically ill OR acutely ill OR intensive care OR critical care OR icu OR coronary care unit OR neurological intermediate care unit))) AND (tw:((randomized OR randomised OR random OR randomly OR controlled OR rct OR placebo OR group OR trial))) AND (instance:"regional") AND (db:("LILACS"))

Appendix 8. Data collection form

TRIAL IDENTIFICATION		
Author and year		
Publication type	**Lead trial:**	**Secondary publ.:** Name of primary publication of the same trial

STUDY ELIGIBILITY

RCT			Relevant participants			Relevant intervention			Relevant outcomes		
Yes	No	Unclear	Yes	No	Unclear	Yes	No	Unclear	Yes	No*	Unclear

*Issue relates to selective reporting when study authors may have taken measurements for particular outcomes but did not report these within the paper(s). Review authors should contact trialists for information on possible non-reported outcomes and reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should be excluded.

DO NOT PROCEED IF ANY OF THE ABOVE ANSWERS IS 'NO'

Include	Exclude
	Record reason for exclusion, which is to be inserted into the 'Table of excluded studies'

PARTICIPANTS	
Eligibility	How was participant eligibility defined?
Age (mean, median, range, etc.)	
Sex of participants (numbers/%, etc.)	
Disease status/type, etc. (if applicable)	
Notes	

INTERVENTIONS	
Experimental intervention	Describe experimental intervention (incl. oxygenation target, oxygen administration system, duration)
Control intervention	Describe control intervention (incl. oxygenation target, oxygen administration system, duration)
Co-interventions (any intervention given equally in both interventions)	Specify any other co-interventions

OTHER TRIAL INFORMATION	
Aim of trial	
Country/Countries	

(Continued)

Trial design (parallel/cross-over)	
Trial duration (intervention and follow-up)	Weeks, months, years, not stated
The trial included only participants admitted to ICU?	
Which targets did the participants actually achieve?	
Withdrawals	Were these described?
Study funding source (Incl. role of funders)	
Possible conflicts of interest (for study authors)	
Other	
Notes	

RISK OF BIAS ASSESSMENT

L: low risk of bias, U: unclear risk of bias, H: high risk of bias

Random sequence generation	
Low risk: if sequence generation is achieved using computer, random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards and throwing dice are also adequate if performed by an independent adjudicator. **Unclear risk**: if the method of randomization is not specified. **High risk**: if the allocation sequence is not random.	**Grade** L / U / H
Support for judgement	

Allocation sequence concealment*	
Low risk: if the allocation of participants is performed by a central independent unit, on-site locked computer, identically looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent investigator. There must be no risk of the investigator knowing the sequence.	**Grade** L / U / H

(Continued)

Unclear risk: if the trial is classified as randomized but the allocation concealment process is not described.

High risk: if the allocation sequence is known to the investigators who assigned participants.

Support for judgement

*Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding

Blinding of participants and personnel	
Person responsible for participant care	Yes / No
Participant	Yes / No
Outcome assessor	Yes / No
Other (please specify)	Yes / No
Low risk: if the participants and the personnel are blinded to treatment allocation and this is described. **Unclear risk**: if the procedure of blinding is insufficiently described or not described at all. **High risk**: if blinding of participants and personnel is not performed.	**Grade** L / U / H
Support for judgement	

Blinding of outcome assessment	
Low risk: if the trial investigators performing the outcome assessments, analyses and calculations are blinded to the intervention. **Unclear risk**: if the procedure of blinding is insufficiently described or not described at all. **High risk**: if blinding of outcome assessment is not performed.	**Grade** L / U / H
Support for judgement	

Incomplete outcome data	
Low risk: there are no dropouts or withdrawals for all outcomes, or the numbers and reasons for the withdrawals and dropouts for all outcomes are clearly stated and can be described as being similar in both groups. As a general rule the trial is judged as at a low risk of bias due to incomplete outcome data if the number of dropouts is less than 5%. However, the 5% cut-off is not definitive.	**Grade** L / U / H

(Continued)

Unclear risk: the numbers and reasons for withdrawals and dropouts are not clearly stated.
High risk: the pattern of dropouts can be described as being different in the two intervention groups or the trial uses improper methodology in dealing with the missing data, e.g. last observation carried forward.

Support for judgement

Selective outcome reporting

Low risk: a protocol is published before or at the time the trial is begun and the outcome called for in the protocol is reported on.
Unclear risk: if there is no protocol and the outcome is not reported on.
High risk: if the outcomes which are called on in a protocol are not reported on.

Grade

L / U / H

Support for judgement

Baseline imbalance

Low risk: no baseline imbalance in important characteristics was noted.

Unclear risk: baseline characteristics were not reported.

High risk: baseline imbalance was due to chance or was due to imbalanced exclusion after randomization.

Grade

L / U / H

Support for judgement

Early stopping

Low risk: sample size calculation was reported and the trial was not stopped, or if the trial was stopped early by formal stopping rules at a point at which the likelihood of observing an extreme intervention effect due to chance was low.

Unclear risk: sample size calculation was not reported, and if it is not clear whether or not the trial was stopped early.

High risk: the trial was stopped early because of informal stopping rules, or if the trial was stopped early by a formal stopping rule at a point at which the likelihood of observing an extreme intervention effect due to chance was high.

Grade

L / U / H

Support for judgement

Other bias risk	
Low risk: the trial appears to be free of other components (e.g. academic bias or for-profit bias) that could put it at risk of bias. **Unclear risk**: the trial may or may not be free of other components that could put it at risk of bias. **High risk**: there are other factors in the trial that could put it at risk of bias (e.g. authors have conducted trials on the same topic, for-profit bias, etc.)	**Grade** L / U / H
Support for judgement	

Overall risk of bias	
Low risk: each outcome result will be classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs are classified as low risk of bias. **High risk**: the outcome result will be classified 'high risk of bias' if any of the bias risk domains described in the above are classified as 'unclear' or 'high risk of bias'. In addition, if one or more of the bias domains described in the above paragraphs are classified as 'unclear' or at 'high risk of bias'.	**Grade** L / H
Support for judgement	

OUTCOMES

PRIMARY OUTCOMES	Available for the trial
All-cause mortality	Yes / No
Number of participants with one or more serious adverse events (dichotomous outcome)	Yes / No
Quality of life	Yes / No

*We used the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event (ICH-GCP 1997), that is, any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity. We will consider all other adverse events as non-serious.

SECONDARY OUTCOMES	Available for the trial
Lung injury*	Yes / No
Acute myocardial infarction**	Yes / No

(Continued)

Stroke**	Yes / No
Severe sepsis**	Yes / No

* Diagnosed after randomization (composite outcome) defined as either ARDS, lung fibrosis, or pulmonary embolism.
** Diagnosed after randomization.

OTHER OUTCOMES OF THE TRIAL	
Additional outcomes	List additional reported outcomes

SUBGROUPS	
Overall risk of bias	High risk of bias
	Low or uncertain risk of bias
According to ICU population	Medical
	Surgical
According to different definitions of oxygen target	Oxygen level measured using FiO_2
	Oxygen level measured using PaO_2
	Oxygen level measured using SaO_2 or SpO_2
	Oxygen level measured using PaO_2 or SaO_2 or SpO_2
According to oxygen delivery system	Invasive mechanical ventilation with endotracheal tube
	Any non-invasive oxygen administration

OUTCOMES						
Follow-up periods	List all follow-up periods given in report					
Total no. of randomized participants	Participants in experimental group			Participants in control group		
Primary outcomes						
(dichotomous 'end point' outcome)		Participants analysed		Number of events in the groups: E = experimental C = control		**Bias of the outcome**
All-cause mortality	Maximum follow-up	E (n)		E (n)		L / U / H
		C (n)		C (n)		
	End of trial intervention period	E (n)		E (n)		L / U / H
		C (n)		C (n)		
Serious adverse events: Nb. Number of counts. If SAE is reported, list them individually	Maximum follow-up	E (n)		E (n)		L / U / H
		C (n)		C (n)		
	End of trial intervention period	E (n)		E (n)		L / U / H
		C (n)		C (n)		
(continuous outcome)		Participants analysed	Mean (endpoint or change)		SD	**Bias of the outcome**
Quality of life: **Type of QoL scale**:	Maximum follow-up	E (n)	E		E	L / U / H
		C (n)	C		C	L / U / H
	End of trial intervention period	E (n)	E		E	L / U / H
		C (n)	C		C	L / U / H

Secondary outcomes				
(dichotomous outcome)		Participants analysed	Number of events in the groups: E = experimental C = control	**Bias of the outcome**
Lung injury	Maximum follow-up	E (n)	E (n)	L / U / H
		C (n)	C (n)	
	End of trial intervention period	E (n)	E (n)	L / U / H
		C (n)	C (n)	
Acute myocardial infarction	Maximum follow-up	E (n)	E (n)	L / U / H
		C (n)	C (n)	
	End of trial intervention period	E (n)	E (n)	L / U / H
		C (n)	C (n)	
Stroke	Maximum follow-up	E (n)	E (n)	L / U / H
		C (n)	C (n)	
	End of trial intervention period	E (n)	E (n)	L / U / H
		C (n)	C (n)	
Severe sepsis	Maximum follow-up	E (n)	E (n)	L / U / H
		C (n)	C (n)	
	End of trial intervention period	E (n)	E (n)	L / U / H
		C (n)	C (n)	

OTHER INFORMATION

Key conclusion of study authors as stated in paper

Information relevant to the results

(Continued)

Indicate if any data were obtained from the primary author; if results were estimated from graphs, etc. or were calculated by you using a formula (should be stated and the formula given). In general, if results not reported in paper(s) are not obtained, this should be made clear here to be cited in the review.

Appendix 9. Criteria for 'Risk of bias' evaluation

Random sequence generation

1. Low risk: if sequence generation is achieved using computer, random number generator, or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are also adequate if performed by an independent adjudicator.
2. Unclear risk: if the method of randomization is not specified.
3. High risk: if the allocation sequence is not random.

Allocation sequence concealment

1. Low risk: if the allocation of participants is performed by a central, independent unit; on-site locked computer; identically appearing, numbered, sealed, opaque envelopes; or drug bottles or containers prepared by an independent investigator. There must be no risk of the investigator knowing the sequence.
2. Unclear risk: if the trial is classified as randomized but the allocation concealment process is not described.
3. High risk: if the allocation sequence is known to the investigators who assigned participants.

Blinding of participants and personnel

1. Low risk: if the participants and personnel are blinded to treatment allocation and this is described.
2. Unclear risk: if the description of the blinding procedure is insufficient or absent.
3. High risk: if blinding of participants and personnel is not performed.

Blinding of outcome assessment

1. Low risk: if the trial investigators performing the outcome assessments, analyses, and calculations are blinded to the intervention.
2. Unclear risk: if the description of the blinding procedure is insufficient or absent.
3. High risk: if blinding of outcome assessment is not performed.

Incomplete outcome data

1. Low risk: there are no dropouts or withdrawals for all outcomes, or the numbers and reasons for withdrawals and dropouts for all outcomes are clearly stated and are described as being similar in both groups. As a general rule, a judgement of low risk of bias is made if the number of dropouts is less than 5%; however, the 5% cut-off is not definitive.
2. Unclear risk: the numbers and reasons for withdrawals and dropouts are not clearly stated.
3. High risk: the pattern of dropouts is described as being different in the two intervention groups, or the trial uses improper methodology in dealing with the missing data, e.g. last observation carried forward.

Selective outcome reporting

1. Low risk: a protocol is published before or at the time the trial is begun, and the outcome called for in the protocol is reported on.
2. Unclear risk: if there is no protocol and the outcome is not reported on.
3. High risk: if the outcomes called for in the protocol are not reported on.

Other bias

1. Low risk: the trial appears to be free of other issues (e.g. academic bias or for-profit bias) that could put it at risk of bias.
2. Unclear risk: the trial may or may not be free of other components that could put it at risk of bias.
3. High risk: there are other factors in the trial that could put it at risk of bias (e.g. authors have conducted trials on the same topic, for-profit bias, etc.).

Overall risk of bias

1. Low risk: the trial will be classified as overall 'low risk of bias' only if all of the 'Risk of bias' domains described above are classified as low risk of bias.
2. High risk: the trial will be classified as overall 'high risk of bias' if any of the 'Risk of bias' domains described above are classified as 'unclear' or 'high risk of bias'.

WHAT'S NEW

Date	Event	Description
27 November 2019	Amended	The ICU-ROX trial (ICU-ROX 2019) was added as a reference awaiting classification. ICU-ROX was published after our literature search was run and thus was not included in this review. The ICU-ROX trial will be included in a review update.

HISTORY

Protocol first published: Issue 4, 2017
Review first published: Issue 11, 2019

Date	Event	Description
27 November 2019	Amended	Author affiliations updated
8 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care
20 September 2017	Amended	We have cited the systematic review Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients (Gilbert-Kawai 2014).

CONTRIBUTIONS OF AUTHORS

Marija Barbateskovic (MB), Olav L Schjørring (OLS), Sara Russo Krauss, (SRK), Janus C Jakobsen (JJ), Christian S Meyhoff (CM), Rikke M Dahl (RD), Bodil S Rasmussen (BR), Anders Perner (AP), Jørn Wetterslev (JW).

Writing first draft protocol and co-ordinating the protocol: MB

Performing search strategies, searches, and analyses: MB

Literature screening and data extraction: MB, OLS, SRK

Writing first draft review: MB

Writing the review: MB, OLS, SRK, JJ, CM, RD, BR, AP, JW

Person responsible for reading and checking the review before submission: MB

DECLARATIONS OF INTEREST

Marija Barbateskovic: Innovation Fund Denmark provided a grant to Center for Research in Intensive Care (CRIC), which made it possible for Copenhagen Trial Unit as a partner of CRIC to write the review during Marija Barbateskovic's PhD study.

Olav L Schjørring: Oliver's PhD study is funded through a grant from the Innovation Fund Denmark. Furthermore, he is the co-ordinating investigator of the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial, a randomized clinical trial comparing a higher versus lower oxygenation target in adult patients with hypoxaemic respiratory failure acutely admitted to the intensive care unit.

Sara Russo Krauss: None known.

Janus C Jakobsen: None known.

Christian S Meyhoff: Dr Meyhoff is the chief investigator for the VitamIn and oXygen Interventions and Cardiovascular Events (VIXIE) trial (a randomized controlled trial comparing perioperative oxygen fractions); site investigator in the HOT-ICU trial (a randomized controlled

trial investigating oxygenation targets in the intensive care unit); co-author of several Cochrane Reviews about oxygen therapy; and was the primary investigator of the PROXI trial (a randomized controlled trial comparing perioperative oxygen fractions).

Rikke M Dahl: None known.

Bodil S Rasmussen: Bodil is the sponsor and primary investigator of a randomized clinical trial comparing a higher versus lower oxygenation target in adult patients with hypoxaemic respiratory failure acutely admitted to the intensive care unit (the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial (NCT03174002)).

Anders Perner: Anders's institution receives money for research from Ferring Pharmaceuticals and the Novo Nordisk Foundation

Jørn Wetterslev: Jørn is a member of the task force on Trial Sequential Analysis (TSA) at the Copenhagen Trial Unit, developing and programming TSA (see www.ctu.dk/tsa). I am a supervisor for PhD student Marija Barbateskovic, and the work concerning this review was paid for in part by a grant from Innovation Fund Denmark.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Innovation Fund Denmark, Denmark.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We changed the title from 'Higher versus lower inspiratory oxygen fraction or targets of arterial oxygenation for adult intensive care patients' to 'Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit'.
2. We used a power of 90%, not 80% as reported in the protocol (Barbateskovic 2017), as a meta-analysis should use higher (or same) power as its included trials in order to communicate the best available evidence.
3. We changed the wording in the Types of interventions section from "the aim of which was exposure to hyperoxaemia" to "the aim of which was exposure to hyperoxia in the lungs".
4. We added the subgroup 'mixed ICU' to the subgroup analysis (including five trials) of ICU setting, as only one trial included adults admitted to a medical ICU and none to a surgical ICU.
5. In our protocol we stated that we would search the Allied and Complementary Medicine Database (AMED) for eligible trials. We had no access to AMED, and so this search was not conducted.
6. We stated in the 'Types of outcome measures' section of the protocol that we would estimate all continuous and dichotomous outcomes at two time points: the time point closest to three months, which was our assessment time point of primary interest; and at maximum follow-up, as reported by trialists. We realized that this information was confusing. We intended for the assessments at maximum follow-up to be considered as a sensitivity analyses, thus we have specified this in the Sensitivity analysis section.
7. We have now precisely defined the analyses estimating the effect of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the proportion of participants with one or more serious adverse events. As the reporting of serious adverse events as a combined outcome was not carried out strictly according to the ICH-GCP recommendation, we estimated the proportion of participants with one or more serious adverse events in a primary analysis: highest proportion of specific serious adverse event reported in each trial. We estimated the effect of higher versus lower inspired fraction or target of oxygen in a sensitivity analysis: the proportion estimated as cumulated number of serious adverse events reported in each trial divided by the number of participants in each intervention group.
8. We have now precisely defined the analyses estimating the effect of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation on the proportion of participants with lung injuries. No trial reported on lung injury as a composite outcome, however some trials reported on ARDS and pneumonia. We estimated the proportion of participants with one or more lung injuries in a primary analysis: highest proportion of specific lung injuries reported in each trial. We estimated the effect of higher versus lower inspired fraction or target of oxygen in a sensitivity analysis: the proportion estimated as cumulated number of lung injuries reported in each trial divided by the number of participants in each intervention group.
9. We changed the wording of the second co-primary outcome (proportion of participants with one or more serious adverse events), without changing the content and implication of the definition.
10. We added a paragraph on Bayes factors in the Methods section. In our protocol, we did not explicitly state that we would present Bayes factors, however we did state that the review would be conducted following the recommendations by Jakobsen and colleagues (Jakobsen 2014a), which include an eight-step assessment involving Bayes factors. In addition, we specified in the Methods section that TSA and calculation of Bayes factors are included in the eight-step assessment.